

JAN

Access DB# 82122

## SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Samuel Wei Lin Examiner #: 79120 Date: 12-1-02  
Art Unit: 1653 Phone Number 306-3413 Serial Number: 09800856  
Mail Box and Bldg/Room Location: 9801 Results Format Preferred (circle): PAPER DISK E-MAIL  
OR 9D06

If more than one search is submitted, please prioritize searches in order of need.

\*\*\*\*\*

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: \_\_\_\_\_

Inventors (please provide full names): \_\_\_\_\_

Earliest Priority Filing Date: 3-5-2001

\*For Sequence Searches Only\* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

please search peptide structure in Claim 1, the limitations  
set forth in claims 2-4 as well (see the attachment).

Thanks.

Sam Lin

Jan Delaval  
Reference Librarian  
Biotechnology & Chemical Library  
CM1 1E07 - 703-308-4498  
jan.delaval@uspto.gov

\*\*\*\*\*  
STAFF USE ONLY

	Type of Search	Vendors and cost where applicable
Searcher: _____	NA Sequence (#) _____	STN _____
Searcher Phone #: _____	AA Sequence (#) _____	Dialog _____
Searcher Location: _____	Structure (#) _____	Questel/Orbit _____
Date Searcher Picked Up: <u>12/1/02</u>	Bibliographic _____	Dr.Link _____
Date Completed: <u>12/12/02</u>	Litigation _____	Lexis/Nexis _____
Searcher Prep & Review Time: _____	Fulltext _____	Sequence Systems _____
Clerical Prep Time: <u>20</u>	Patent Family _____	WWW/Internet _____
Online Time: <u>+ 80</u>	Other _____	Other (specify) _____

=> fil reg

FILE 'REGISTRY' ENTERED AT 15:34:17 ON 12 DEC 2002

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 11 DEC 2002 HIGHEST RN 475975-25-8

DICTIONARY FILE UPDATES: 11 DEC 2002 HIGHEST RN 475975-25-8

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:

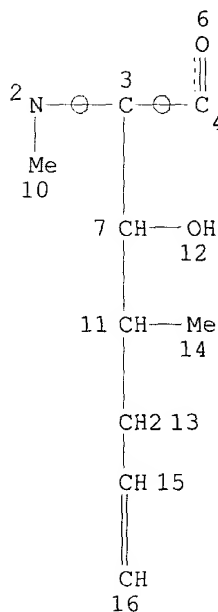
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=> d sta que 137

L7 21 SEA FILE=REGISTRY ABB=ON PLU=ON (100364-58-7/BI OR 122547-85-7/BI OR 172222-30-9/BI OR 223415-64-3/BI OR 457612-98-5/BI OR 457612-99-6/BI OR 457613-00-2/BI OR 457613-01-3/BI OR 457613-02-4/BI OR 457613-03-5/BI OR 457613-04-6/BI OR 457613-05-7/BI OR 457613-06-8/BI OR 457613-07-9/BI OR 457613-08-0/BI OR 457613-09-1/BI OR 457613-10-4/BI OR 457613-11-5/BI OR 59865-13-3/BI OR 624-48-6/BI OR 96-33-3/BI)

L8 17 SEA FILE=REGISTRY ABB=ON PLU=ON L7 AND SQL/FA

L9 STR



Jan Delaval  
Reference Librarian  
Biotechnology & Chemical Library  
CM1 1E07 - 703-309-4488  
[jan.delaval@usplo.gov](mailto:jan.delaval@usplo.gov)

NODE ATTRIBUTES:

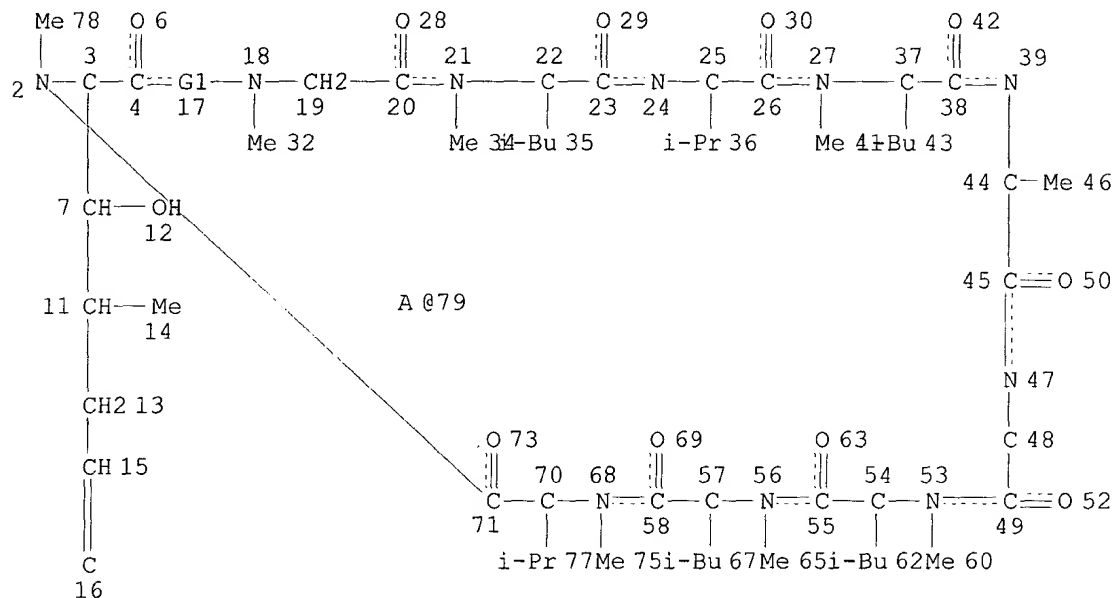
DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
RING(S) ARE ISOLATED OR EMBEDDED  
NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE

L11 685 SEA FILE=REGISTRY SSS FUL L9  
L12 727 SEA FILE=REGISTRY ABB=ON PLU=ON ['ABU''NVA'VT]'SAR'LVLA[AS]LL  
V/SQSP  
L13 342 SEA FILE=REGISTRY ABB=ON PLU=ON L11 AND L12  
L14 342 SEA FILE=REGISTRY ABB=ON PLU=ON L13 AND 11/SQL  
L15 STR



REP G1=(3-10) 79

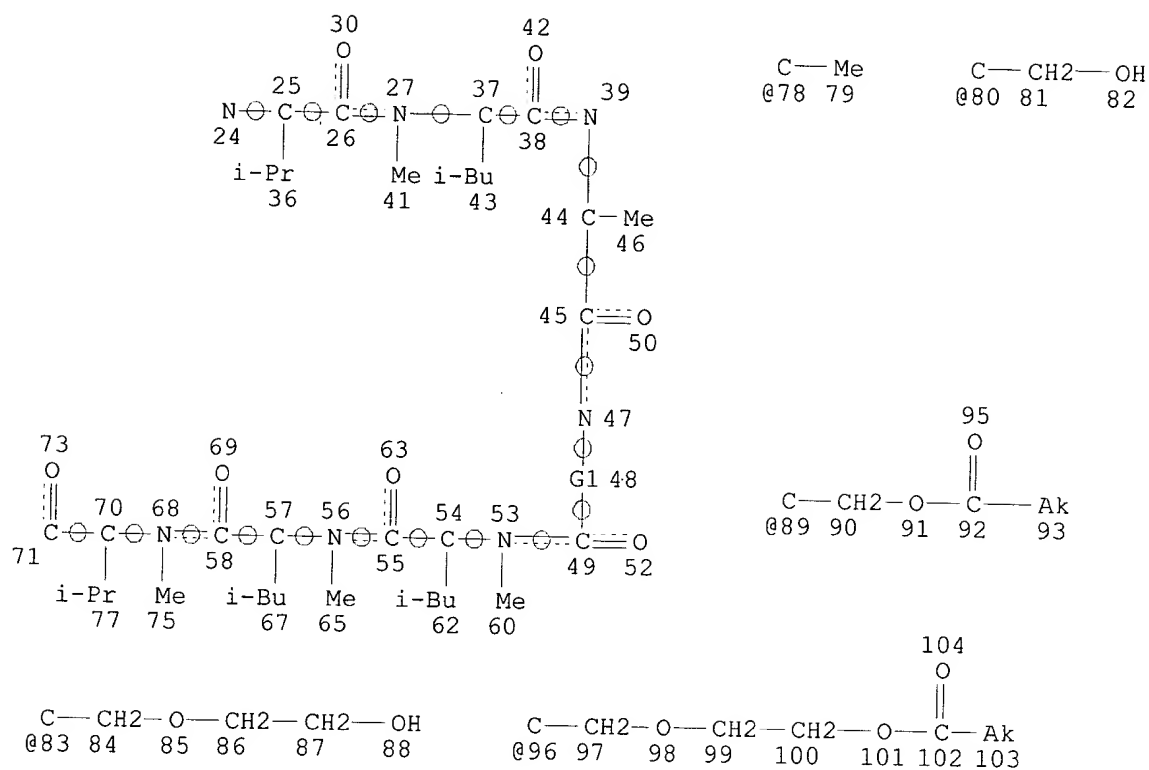
NODE ATTRIBUTES:

CONNECT IS M1 RC AT 16  
CONNECT IS M1 RC AT 48  
CONNECT IS M1 RC AT 79  
DEFAULT MLEVEL IS ATOM  
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
RING(S) ARE ISOLATED OR EMBEDDED  
NUMBER OF NODES IS 63

STEREO ATTRIBUTES: NONE

L17 224 SEA FILE=REGISTRY SUB=L14 CSS FUL L15  
L18 STR



VAR G1=78/80/89/83/96

NODE ATTRIBUTES:

CONNECT IS M1 RC AT 24

CONNECT IS M1 RC AT 71

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

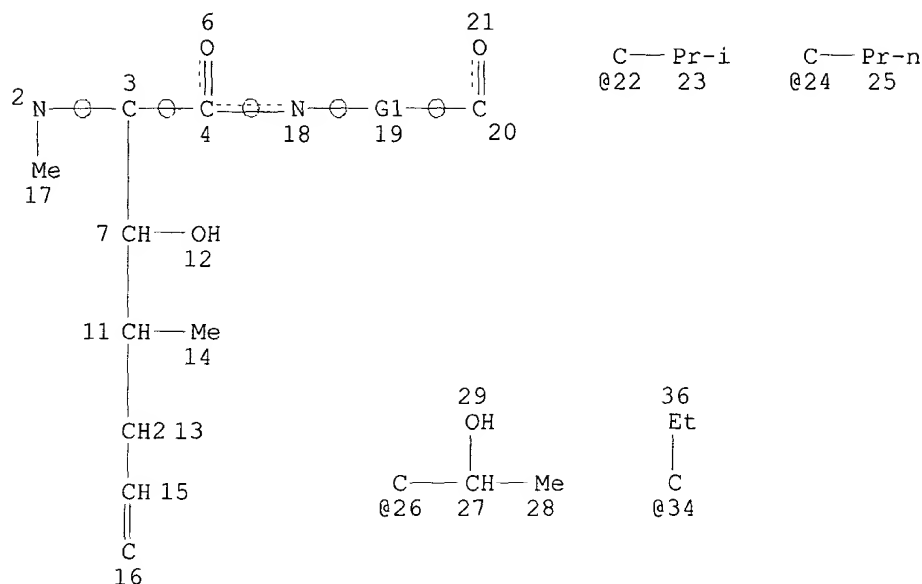
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 64

STEREO ATTRIBUTES: NONE

L20 166 SEA FILE=REGISTRY SUB=L17 CSS FUL L18

L25 STR



VAR G1=34/22/26/24

NODE ATTRIBUTES:

CONNECT IS M1 RC AT 2

CONNECT IS M1 RC AT 16

CONNECT IS M1 RC AT 20

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 26

STEREO ATTRIBUTES: NONE

L26 126 SEA FILE=REGISTRY SUB=L20 SSS FUL L25  
 L27 11 SEA FILE=REGISTRY ABB=ON PLU=ON L26 AND (LABELED OR IDS/CI  
 OR (D OR T)/ELS OR 11C# OR 13C# OR 14C# OR C11# OR C13# OR  
 C14#)  
 L28 115 SEA FILE=REGISTRY ABB=ON PLU=ON L26 NOT L27  
 L29 27 SEA FILE=REGISTRY ABB=ON PLU=ON L28 AND NC>=2  
 L30 21 SEA FILE=REGISTRY ABB=ON PLU=ON L28 AND NR>=3  
 L31 82 SEA FILE=REGISTRY ABB=ON PLU=ON L28 NOT (L29 OR L30)  
 L32 1 SEA FILE=REGISTRY ABB=ON PLU=ON L31 AND MULTICHAIN/NTE  
 L33 81 SEA FILE=REGISTRY ABB=ON PLU=ON L31 NOT L32  
 L34 65 SEA FILE=REGISTRY ABB=ON PLU=ON L33 NOT L8  
 L35 12 SEA FILE=REGISTRY ABB=ON PLU=ON L34 AND (C64H113N11O15 OR  
 C69H114N12O17 OR C68H116N12O16 OR C65H115N11O15 OR C64H113N11O1  
 6 OR C64H113N11O14)  
 L36 4 SEA FILE=REGISTRY ABB=ON PLU=ON L35 NOT (101531-57-1/BI OR  
 101531-89-9/BI OR 158805-69-7/BI OR 158805-72-2/BI OR 158805-75  
 -5/BI OR 158805-76-6/BI OR 158851-25-3/BI OR 220871-49-8/BI)  
 L37 3 SEA FILE=REGISTRY ABB=ON PLU=ON L36 NOT 158805-81-3/BI

=> d his

(FILE 'HCAPLUS' ENTERED AT 14:18:09 ON 12 DEC 2002)

DEL HIS

E OR Y/AU

L1 105 S E4-E8

L2           E LAZAROVA T/AU  
           30 S E3-E11  
           E ENANTA/PA,CS  
 L3           13 S E3-E9  
 L4           137 S L1-L3  
 L5           5 S L4 AND ?CYCLOSPOR?  
           SEL DN AN 1 2  
 L6           2 S L5 AND E1-E4  
           SEL RN

FILE 'REGISTRY' ENTERED AT 14:21:00 ON 12 DEC 2002

L7           21 S E5-E25  
 L8           17 S L7 AND SQL/FA  
 L9           STR  
 L10          32 S L9  
 L11          685 S L9 FUL  
           SAV L11 LIU800/A  
 L12          727 S ['ABU' 'NVA'VT]'SAR'LVLA[AS]LLV/SQSP  
 L13          342 S L11 AND L12  
 L14          342 S L13 AND 11/SQL  
 L15          STR L9  
 L16          11 S L15 CSS SAM SUB=L14  
 L17          224 S L15 CSS FUL SUB=L14  
           SAV L17 LIU800A/A  
 L18          STR L15  
 L19          9 S L18 CSS SAM SUB=L17  
 L20          166 S L18 CSS FUL SUB=L17  
           SAV L20 LIU800B/A  
 L21          STR L9  
 L22          STR L21  
 L23          0 S L22 SAM SUB=L20  
 L24          2 S L22 FUL SUB=L20  
 L25          STR L22  
 L26          126 S L25 FUL SUB=L20  
           SAV L26 LIU800C/A  
 L27          11 S L26 AND (LABELED OR IDS/CI OR (D OR T)/ELS OR 11C# OR 13C# OR  
 L28          115 S L26 NOT L27  
 L29          27 S L28 AND NC>=2  
 L30          21 S L28 AND NR>=3  
 L31          82 S L28 NOT L29,L30  
 L32          1 S L31 AND MULTICHAIN/NTE  
 L33          81 S L31 NOT L32  
 L34          65 S L33 NOT L8  
 L35          12 S L34 AND (C64H113N11O15 OR C69H114N12O17 OR C68H116N12O16 OR C  
           SEL RN L35 2 5 7-12  
 L36          4 S L35 NOT E26-E33  
           SEL RN 4  
 L37          3 S L36 NOT E34  
 L38          20 S L8,L37  
           SAV L38 LIU800D/A

FILE 'HCAOLD' ENTERED AT 15:32:02 ON 12 DEC 2002

L39          0 S L38

FILE 'USPATFULL, USPAT2' ENTERED AT 15:32:05 ON 12 DEC 2002

FILE 'REGISTRY' ENTERED AT 15:32:24 ON 12 DEC 2002

          SEL RN L8 17  
 L40          16 S L8 NOT E35

FILE 'HCAPLUS' ENTERED AT 15:32:57 ON 12 DEC 2002

L41          29 S L40 OR L37  
 L42          1 S L41 AND L4

L43 28 S L41 AND (PD<=20010305 OR PRD<=20010305 OR AD<=20010305)  
 L44 29 S L41-L43

L45 FILE 'USPATFULL, USPAT2' ENTERED AT 15:33:58 ON 12 DEC 2002  
 3 S L40 OR L37

FILE 'REGISTRY' ENTERED AT 15:34:17 ON 12 DEC 2002

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L37 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2002 ACS  
 RN 442912-25-6 REGISTRY  
 CN Cyclosporin A, 6-[(2S,3R,4R,6E)-10-[(2,5-dioxo-1-pyrrolidinyl)oxy]-3-hydroxy-4-methyl-2-(methylamino)-10-oxo-6-decenoic acid]- (9CI) (CA INDEX NAME)  
 FS PROTEIN SEQUENCE; STEREOSEARCH  
 SQL 11  
 NTE cyclic  
 modified (modifications unspecified)

type	location	description
uncommon	Aaa-1	-
uncommon	Abu-2	-
uncommon	Sar-3	-
stereo	Ala-8	D

SEQ 1 XXXLVLAALL V

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

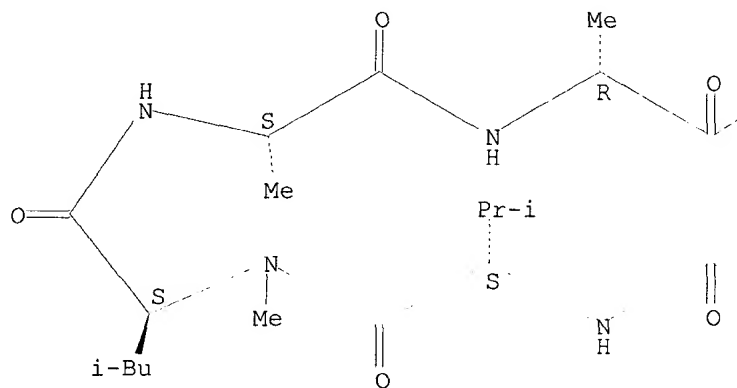
MF C68 H116 N12 O16

SR CA

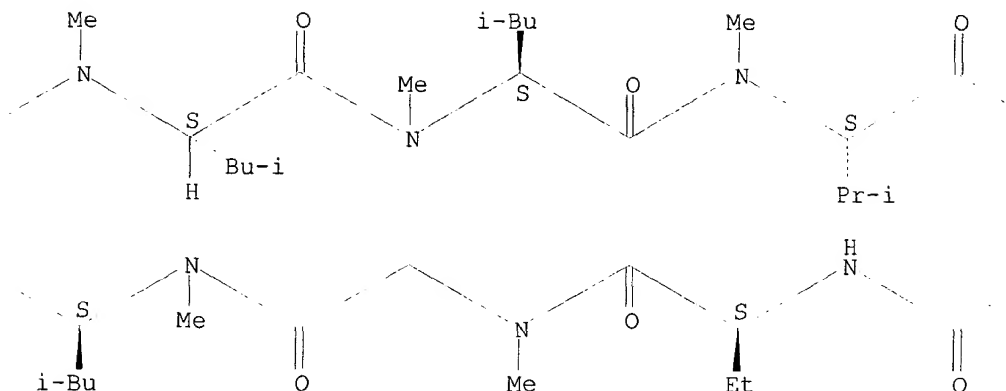
LC STN Files: CA, CAPLUS

Absolute stereochemistry.  
 Double bond geometry as shown.

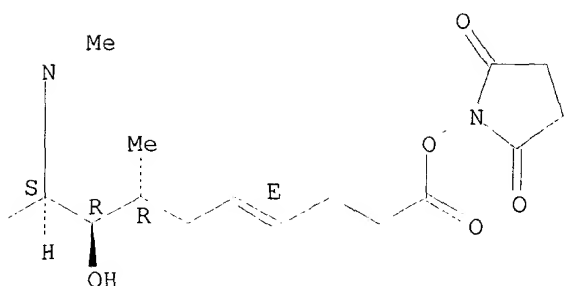
PAGE 1-A



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1 REFERENCES IN FILE CA (1962 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:105954

L37 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2002 ACS

RN 219740-62-2 REGISTRY

CN Cyclo[L-alanyl-O-(2-hydroxyethyl)-D-seryl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-(2S,3R,4R,6E)-7-carboxy-3-hydroxy-4-methyl-2-(methylamino)-6-heptenoyl-(2S)-2-aminobutanoyl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl] (9CI) (CA INDEX NAME)

FS PROTEIN SEQUENCE; STEREOSEARCH

SQL 11

NTE cyclic

modified (modifications unspecified)

type	location	description
uncommon	Aaa-1	-
uncommon	Abu-2	-
uncommon	Sar-3	-

SEQ 1 XXXLVLASLL V



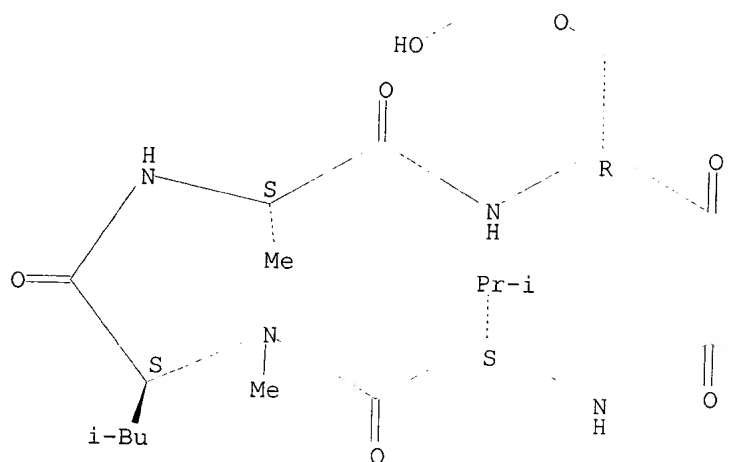
MF C64 H113 N11 O16

SR CA

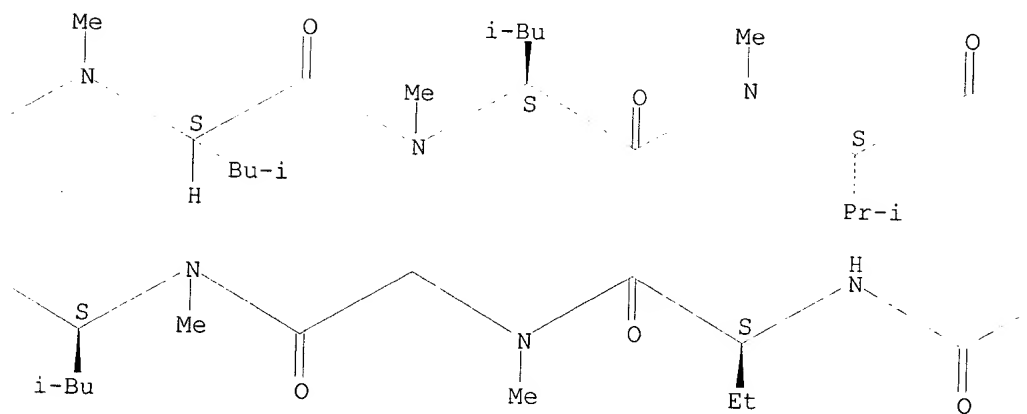
LC STN Files: CA, CAPLUS

Double bond geometry as shown.

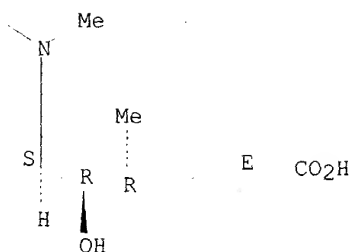
PAGE 1-A



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1 REFERENCES IN FILE CA (1962 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 130:119267

L37 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2002 ACS  
 RN 177080-78-3 REGISTRY  
 CN Cyclosporin A, 6-[(3R,4R,6E)-9-carboxy-6,7-didehydro-3-hydroxy-N,4-dimethyl-L-2-aminononanoic acid]- (9CI) (CA INDEX NAME)  
 FS PROTEIN SEQUENCE; STEREOSEARCH  
 SQL 11  
 NTE cyclic  
 modified (modifications unspecified)

type	location	description
uncommon	Aaa-1	-
uncommon	Abu-2	-
uncommon	Sar-3	-

SEQ 1 XXXLVLAALL V

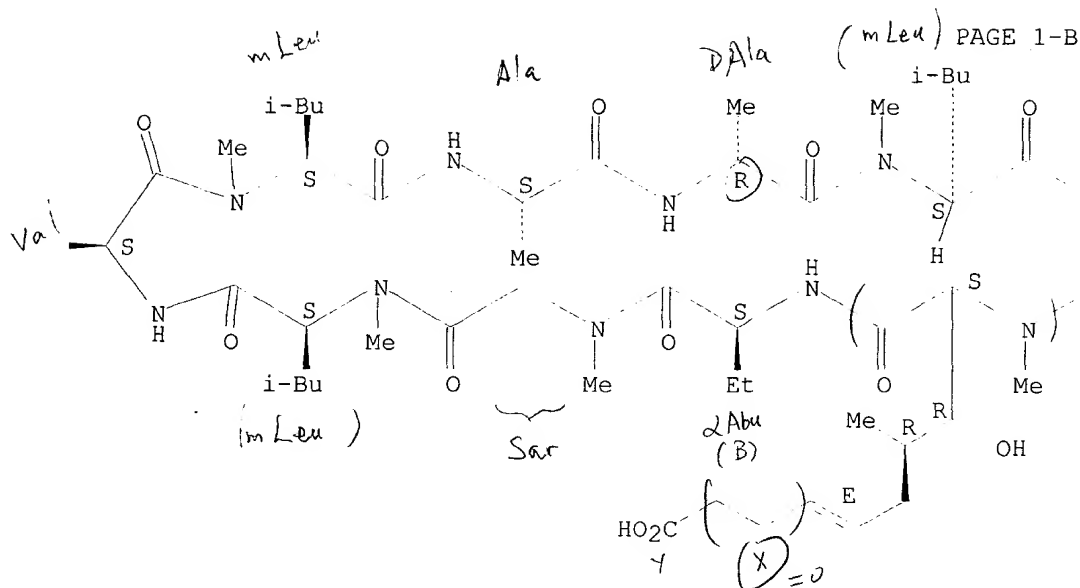
\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

MF C64 H113 N11 O14  
 SR CA  
 LC STN Files: CA, CAPLUS

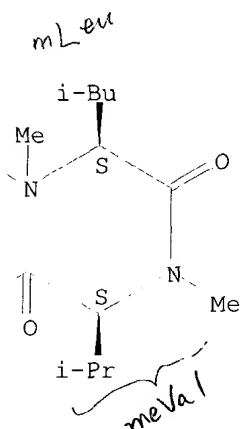
Absolute stereochemistry.  
 Double bond geometry as shown.

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i-Pr



PAGE 1-C



1 REFERENCES IN FILE CA (1962 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 125:6043

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L8 ANSWER 1 OF 17 REGISTRY COPYRIGHT 2002 ACS  
 RN 457613-11-5 REGISTRY  
 CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, anhydride with 9H-fluoren-9-ylmethyl hydrogen carbonate (9CI) (CA INDEX NAME)  
 FS PROTEIN SEQUENCE; STEREOSEARCH  
 SQL 11  
 NTE cyclic  
 modified (modifications unspecified)

type	location	description
uncommon	Aaa-1	-

uncommon	Abu-2	-	-
uncommon	Sar-3	-	-
stereo	Ala-8	-	D

---

SEQ 1 XXXLVLAALL V

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

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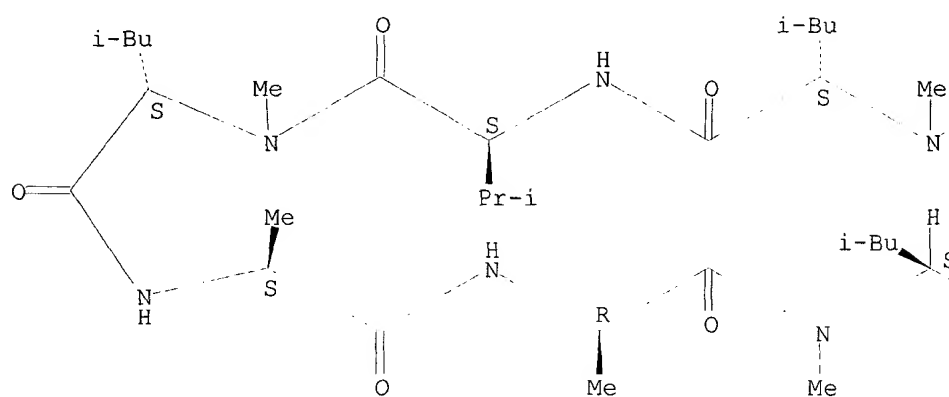
SR CA

LC STN Files: CA, CAPLUS, USPATFULL

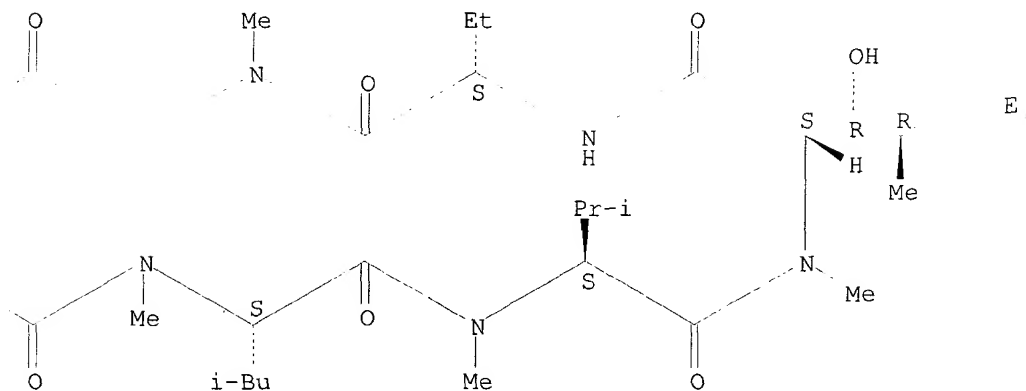
Absolute stereochemistry.

Double bond geometry as shown.

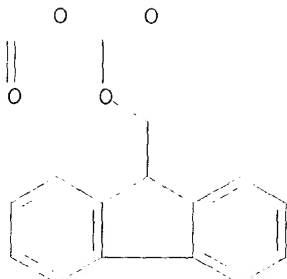
PAGE 1-A



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\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1 REFERENCES IN FILE CA (1962 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 2 OF 17 REGISTRY COPYRIGHT 2002 ACS  
 RN 457613-10-4 REGISTRY  
 CN Cyclosporin A, 6-[(5E,8R,9R,10S)-9-hydroxy-8-methyl-10-(methylamino)-5-undecenedioic acid]-, methyl ester (9CI) (CA INDEX NAME)  
 FS PROTEIN SEQUENCE; STEREOSEARCH  
 SQL 11  
 NTE cyclic  
 modified (modifications unspecified)

type	location			description
uncommon	Aaa-1	-	-	
uncommon	Abu-2	-	-	
uncommon	Sar-3	-	-	
stereo	Ala-8	-	D	

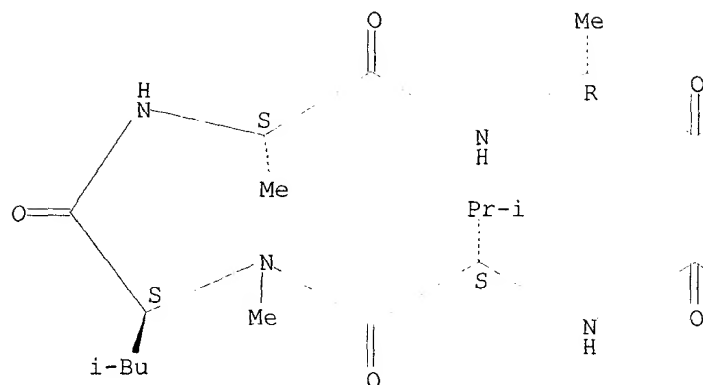
SEQ 1 XXXLVLAALL V

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

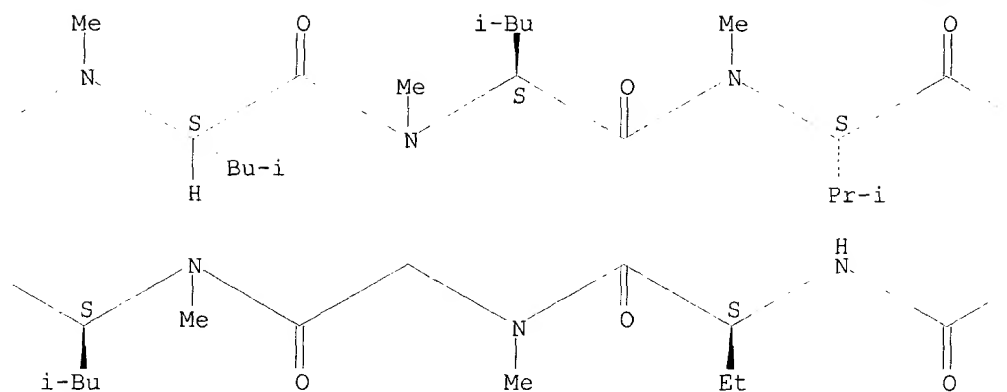
MF C66 H117 N11 O14  
 SR CA  
 LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.  
 Double bond geometry as shown.

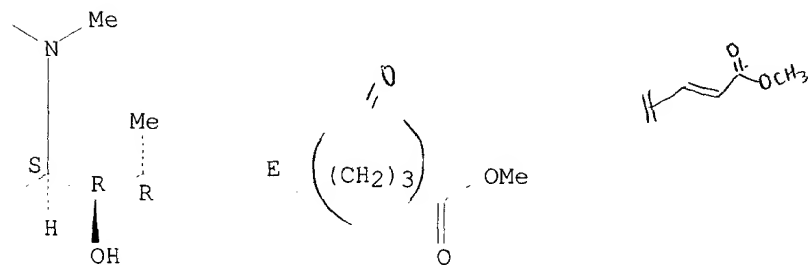
PAGE 1-A



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1 REFERENCES IN FILE CA (1962 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 3 OF 17 REGISTRY COPYRIGHT 2002 ACS  
 RN **457613-09-1** REGISTRY  
 CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-8-oxo-8-  
 [(phenylmethyl)thio]-6-octenoic acid]- (9CI) (CA INDEX NAME)  
 FS PROTEIN SEQUENCE; STEREOSEARCH  
 SQL 11  
 NTE cyclic  
 modified (modifications unspecified)

type	location			description
uncommon	Aaa-1	-	-	
uncommon	Abu-2	-	-	
uncommon	Sar-3	-	-	
stereo	Ala-8	-	D	

SEQ 1 XXXLVLAALL V

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

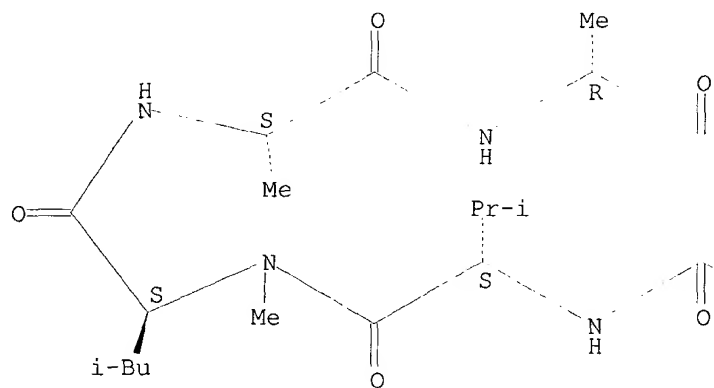
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SR CA

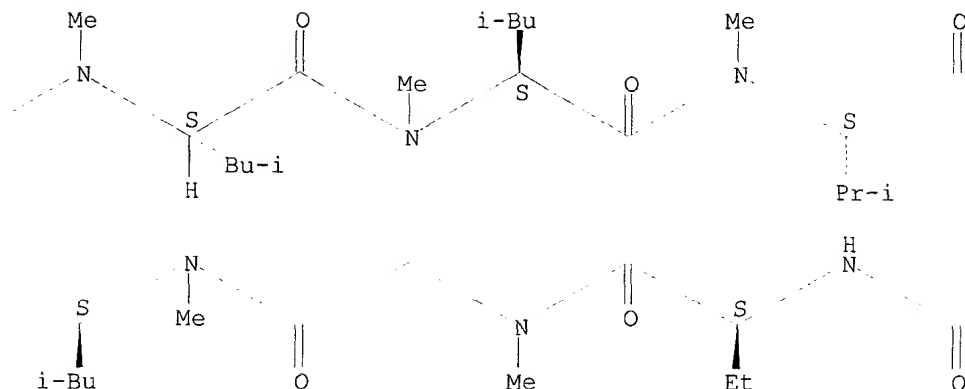
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.  
 Double bond geometry as shown.

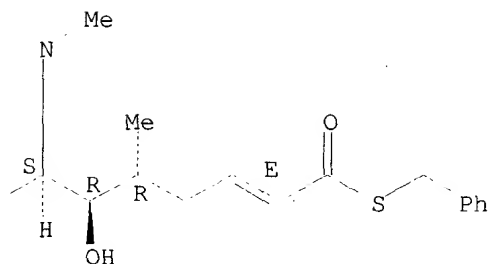
PAGE 1-A



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1 REFERENCES IN FILE CA (1962 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 4 OF 17 REGISTRY COPYRIGHT 2002 ACS

RN 457613-08-0 REGISTRY

CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, (2-methoxyethoxy)methyl ester (9CI) (CA INDEX NAME)

FS PROTEIN SEQUENCE; STEREOSEARCH

SQL 11

NTE cyclic

modified (modifications unspecified)

type	-----	location	-----	description
uncommon	Aaa-1	-	-	
uncommon	Abu-2	-	-	
uncommon	Sar-3	-	-	
stereo	Ala-8	-	D	

SEQ 1 XXXLVLAALL V

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

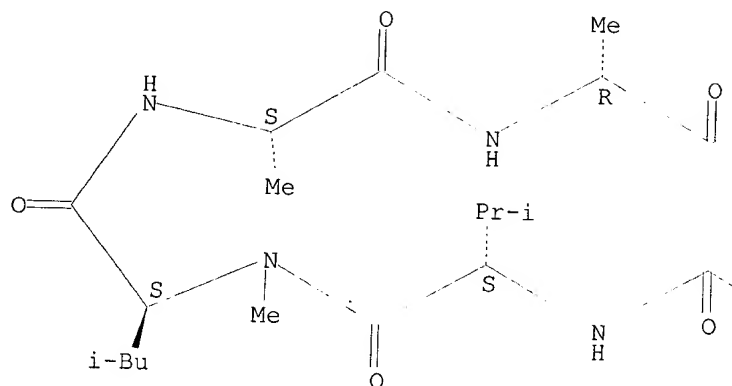


SR CA

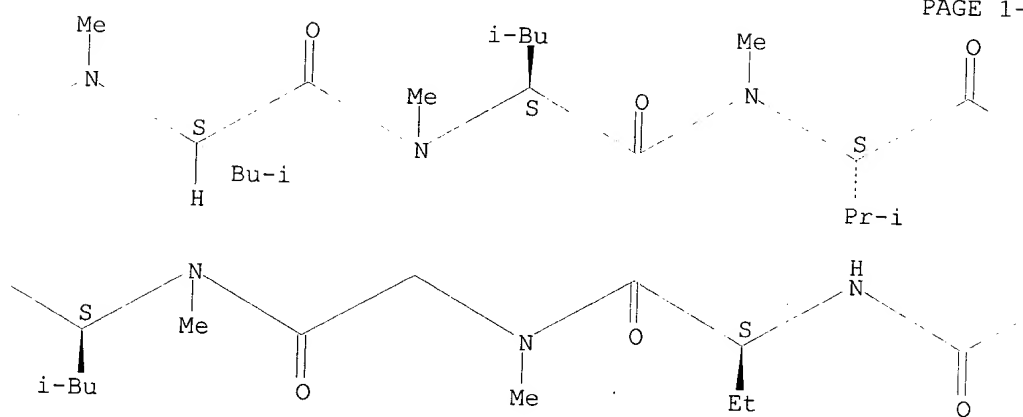
Absolute stereochemistry.

Double bond geometry as shown.

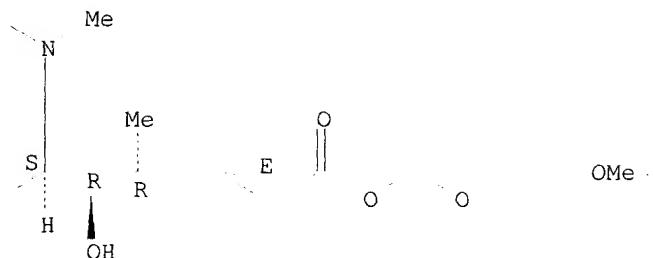
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1 REFERENCES IN FILE CA (1962 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 5 OF 17 REGISTRY COPYRIGHT 2002 ACS  
 RN **457613-07-9** REGISTRY  
 CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, methoxymethyl ester (9CI) (CA INDEX NAME)  
 FS PROTEIN SEQUENCE; STEREOSEARCH  
 SQL **11**  
 NTE cyclic  
 modified (modifications unspecified)

type	location			description
uncommon	Aaa-1	-	-	
uncommon	Abu-2	-	-	
uncommon	Sar-3	-	-	
stereo	Ala-8	-	-	D

SEQ 1 XXXLVLAALL V

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

MF C64 H113 N11 O15

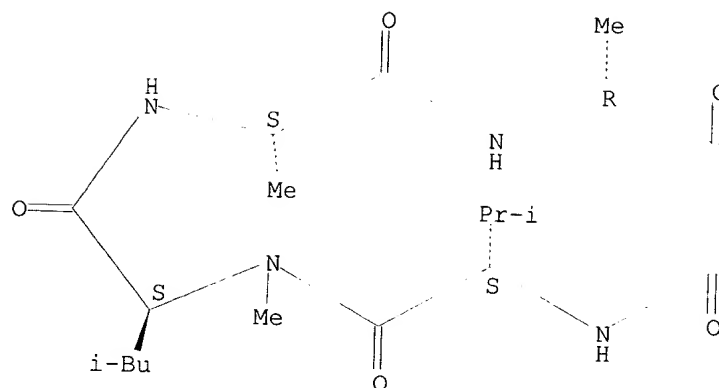
SR CA

LC STN Files: CA, CAPLUS, USPATFULL

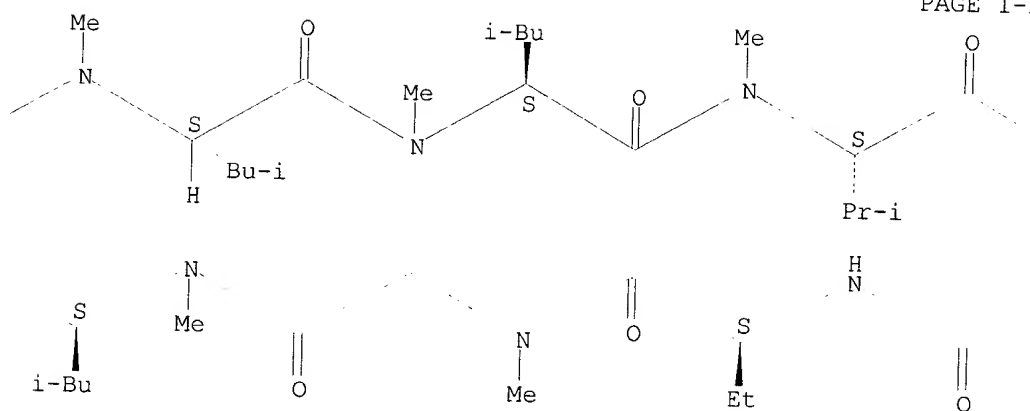
Absolute stereochemistry.

Double bond geometry as shown.

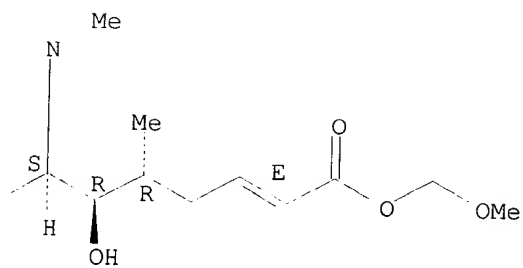
PAGE 1-A



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PAGE 1-C



1 REFERENCES IN FILE CA (1962 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 6 OF 17 REGISTRY COPYRIGHT 2002 ACS  
 RN 457613-06-8 REGISTRY  
 CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, chloromethyl ester (9CI) (CA INDEX NAME)  
 FS PROTEIN SEQUENCE; STEREOSEARCH  
 SQL 11  
 NTE cyclic  
 modified (modifications unspecified)

type	location			description
uncommon	Aaa-1	-	-	
uncommon	Abu-2	-	-	
uncommon	Sar-3	-	-	
stereo	Ala-8	-	D	

SEQ 1 XXXLVLAALL V

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

MF C63 H110 Cl N11 O14

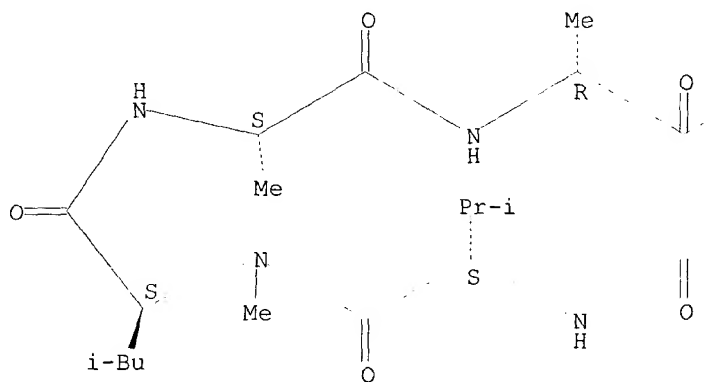
SR CA

LC STN Files: CA, CAPLUS, USPATFULL

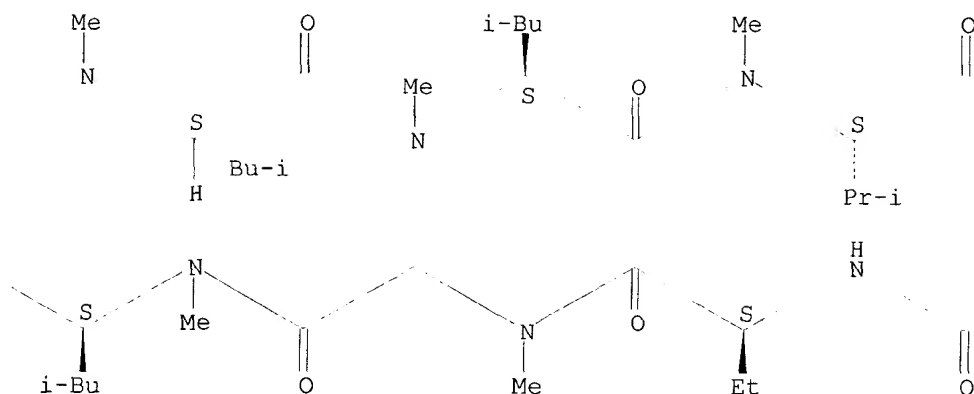
Absolute stereochemistry.

Double bond geometry as shown.

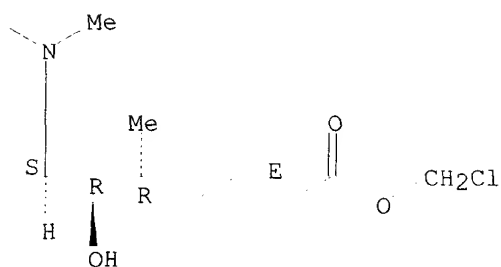
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PAGE 1-B



PAGE 1-C



1 REFERENCES IN FILE CA (1962 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 7 OF 17 REGISTRY COPYRIGHT 2002 ACS  
 RN 457613-05-7 REGISTRY  
 CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, 2,2,2-trifluoroethyl ester (9CI) (CA INDEX NAME)  
 FS PROTEIN SEQUENCE; STEREOSEARCH  
 SQL 11  
 NTE cyclic  
 modified (modifications unspecified)

type	-----	location	-----	description
uncommon		Aaa-1	-	-
uncommon		Abu-2	-	-
uncommon		Sar-3	-	-
stereo		Ala-8	-	D

SEQ 1 XXXLVLAALL V

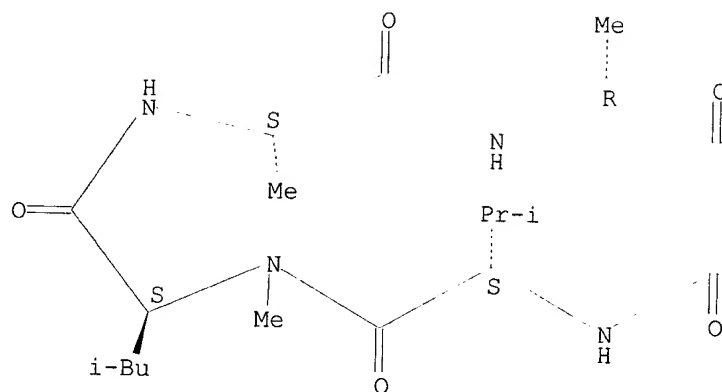
\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

SR CA

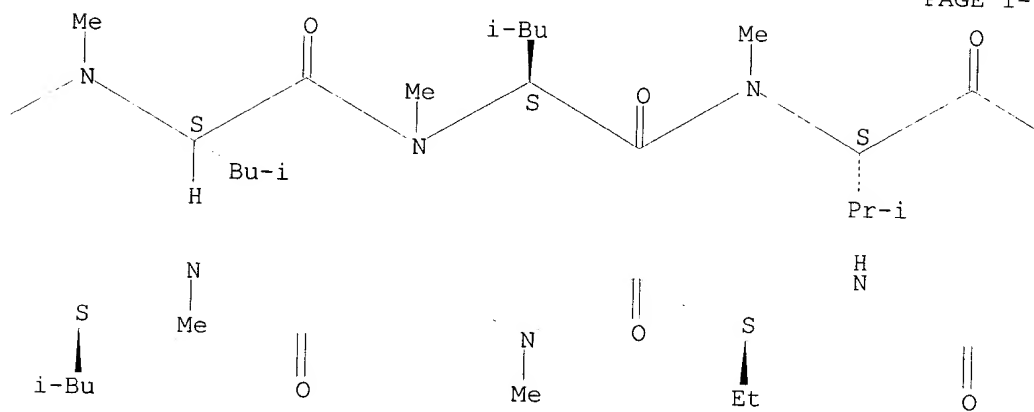
LC STN Files: CA, CAPLUS, USPATFULL

Double bond geometry as shown.

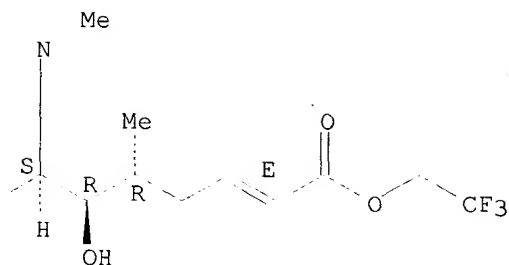
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1 REFERENCES IN FILE CA (1962 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 8 OF 17 REGISTRY COPYRIGHT 2002 ACS

RN 457613-04-6 REGISTRY

CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, trifluoromethyl ester (9CI) (CA INDEX NAME)

FS PROTEIN SEQUENCE; STEREOSEARCH

SQL 11

NTE cyclic

modified (modifications unspecified)

type	----- location -----	description	
uncommon	Aaa-1	-	-
uncommon	Abu-2	-	-
uncommon	Sar-3	-	-
stereo	Ala-8	-	D

SEQ 1 XXXLVLAALL V

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

MF C63 H108 F3 N11 O14

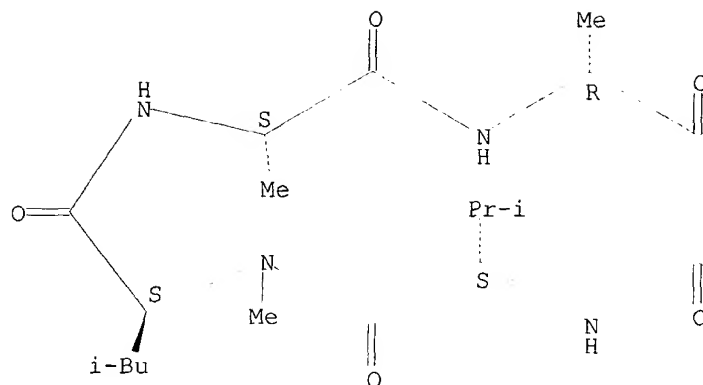
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LC STN Files: CA, CAPLUS, USPATFULL

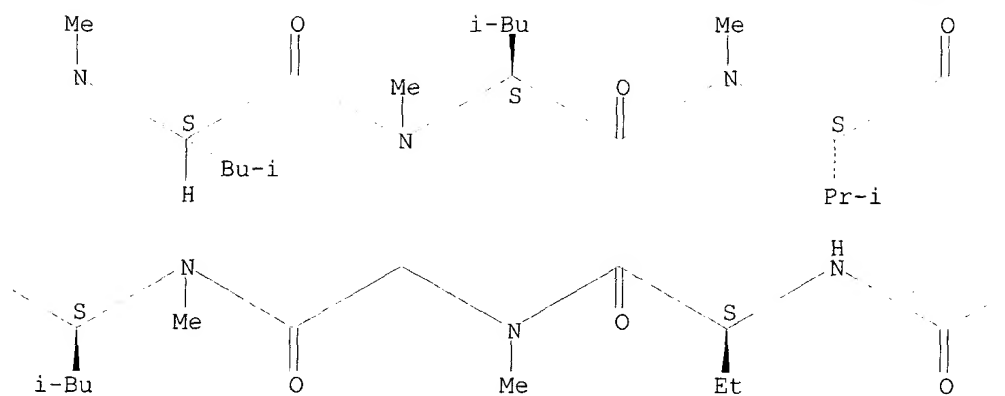
Absolute stereochemistry.

Double bond geometry as shown.

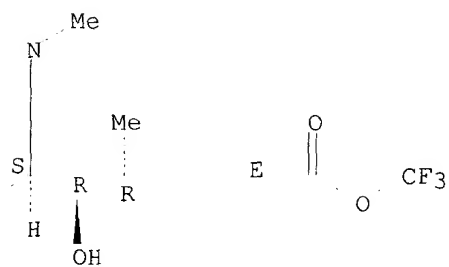
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PAGE 1-B



PAGE 1-C



1 REFERENCES IN FILE CA (1962 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601



L8 ANSWER 9 OF 17 REGISTRY COPYRIGHT 2002 ACS  
 RN 457613-03-5 REGISTRY  
 CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, difluoromethyl ester (9CI) (CA INDEX NAME)  
 FS PROTEIN SEQUENCE; STEREOSEARCH  
 SQL 11  
 NTE cyclic  
 modified (modifications unspecified)

type	location			description
uncommon	Aaa-1	-	-	
uncommon	Abu-2	-	-	
uncommon	Sar-3	-	-	
stereo	Ala-8	-	D	

SEQ 1 XXXLVLAALL V

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

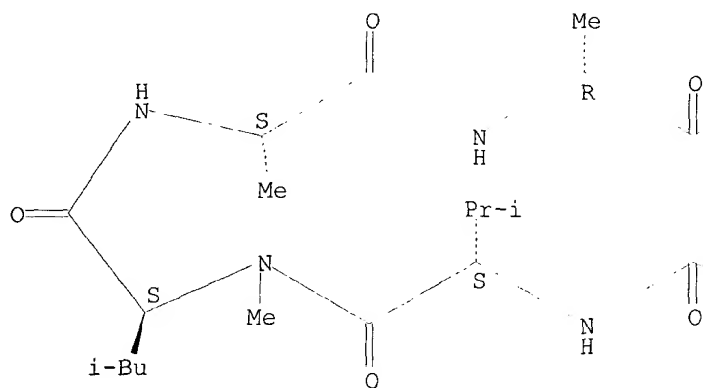
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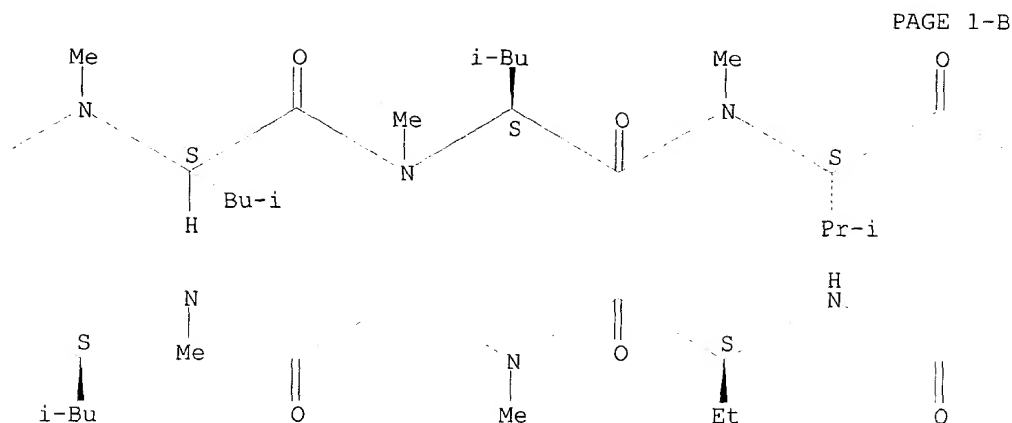
SR CA

LC STN Files: CA, CAPLUS, USPATFULL

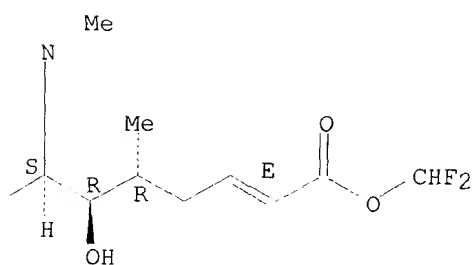
Absolute stereochemistry.  
 Double bond geometry as shown.

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PAGE 1-C



1 REFERENCES IN FILE CA (1962 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 10 OF 17 REGISTRY COPYRIGHT 2002 ACS  
 RN **457613-02-4** REGISTRY  
 CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, fluoromethyl ester (9CI) (CA INDEX NAME)  
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 NTE cyclic  
 modified (modifications unspecified)

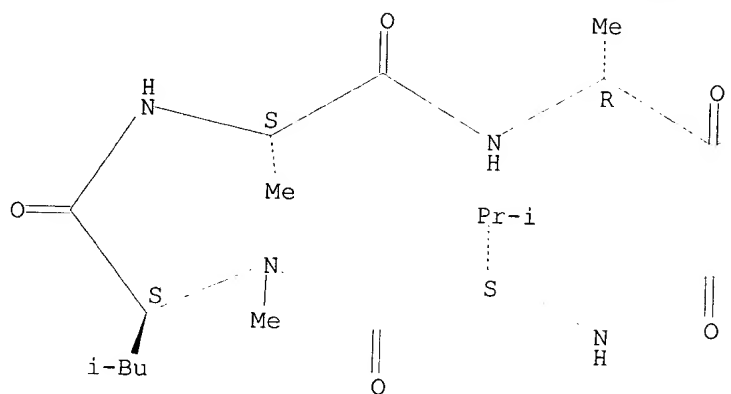
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uncommon	Abu-2	-
uncommon	Sar-3	-
stereo	Ala-8	D

SEQ 1 XXXLVLAALL V

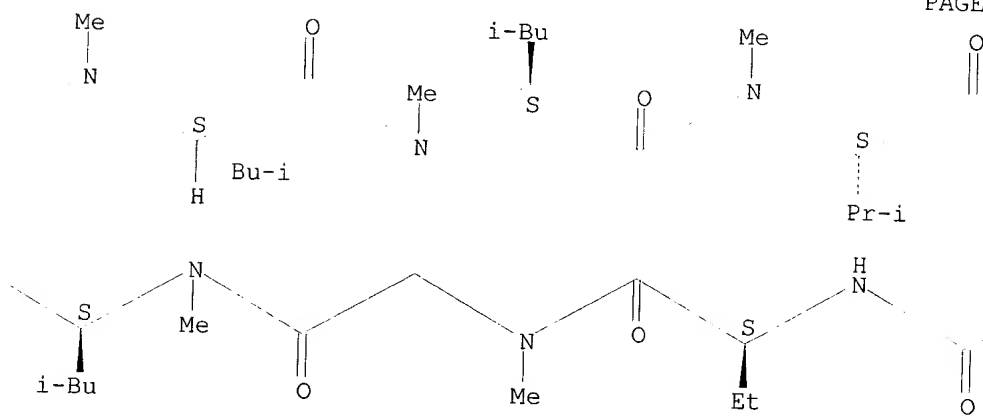
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Absolute stereochemistry.  
Double bond geometry as shown.

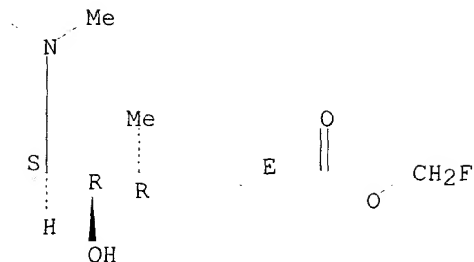
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PAGE 1-B



PAGE 1-C



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 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 11 OF 17 REGISTRY COPYRIGHT 2002 ACS  
 RN 457613-01-3 REGISTRY  
 CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, phenylmethyl ester (9CI) (CA INDEX NAME)  
 FS PROTEIN SEQUENCE; STEREOSEARCH  
 SQL 11  
 NTE cyclic  
 modified (modifications unspecified)

type	location			description
uncommon	Aaa-1	-	-	
uncommon	Abu-2	-	-	
uncommon	Sar-3	-	-	
stereo	Ala-8	-	D	

SEQ 1 XXXLVLAALL V

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

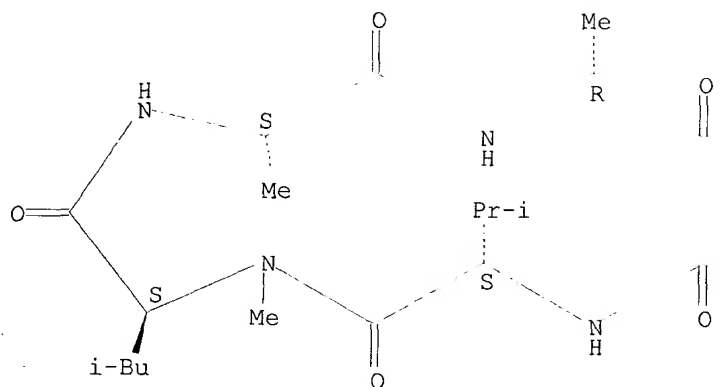
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SR CA

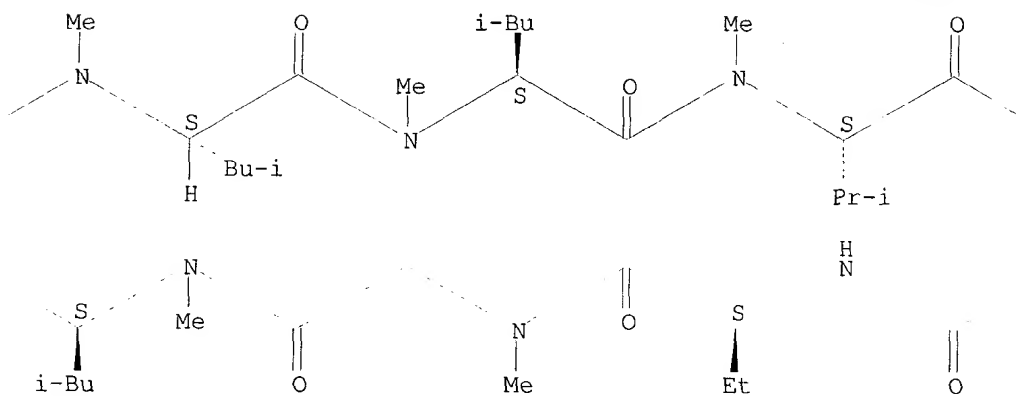
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.  
 Double bond geometry as shown.

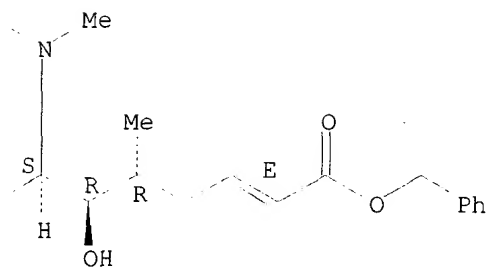
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PAGE 1-C



1 REFERENCES IN FILE CA (1962 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 12 OF 17 REGISTRY COPYRIGHT 2002 ACS  
 RN 457613-00-2 REGISTRY  
 CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, propyl ester (9CI) (CA INDEX NAME)  
 FS PROTEIN SEQUENCE; STEREOSEARCH  
 SQL 11  
 NTE cyclic  
 modified (modifications unspecified)

type	location			description
uncommon	Aaa-1	-	-	
uncommon	Abu-2	-	-	
uncommon	Sar-3	-	-	
stereo	Ala-8	-	D	

SEQ 1 XXXLVL AALL V

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

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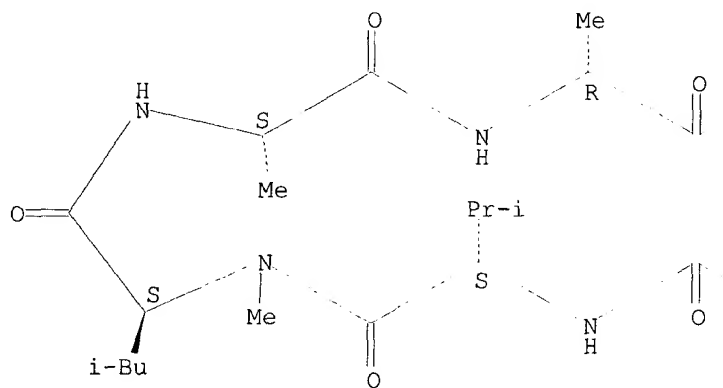
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LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

Double bond geometry as shown.

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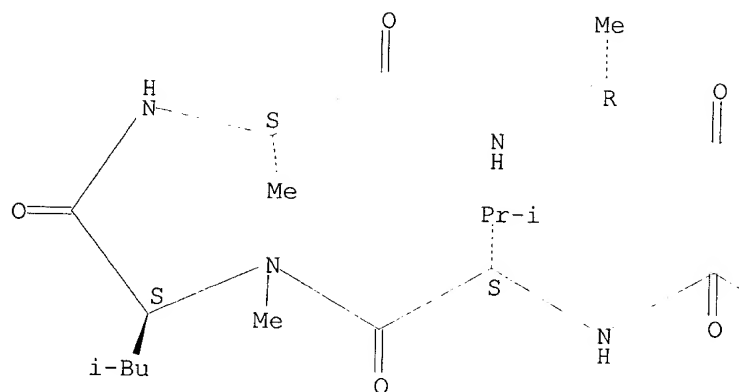




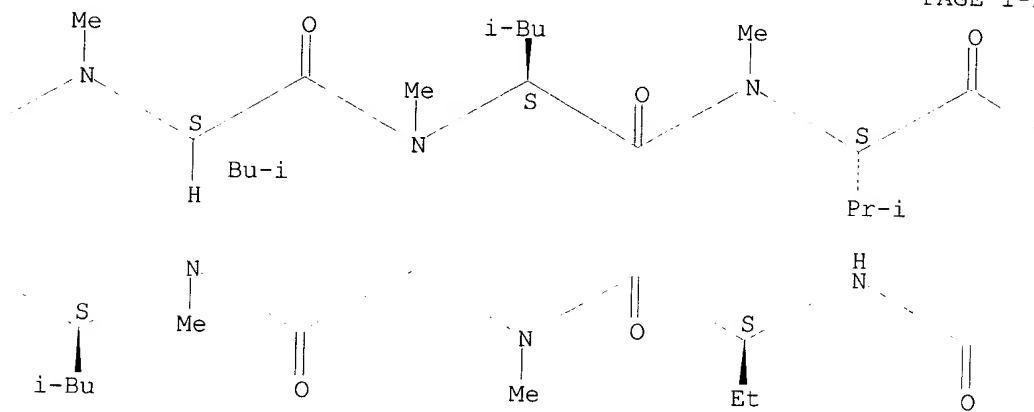
MF C66 H117 N11 O14  
SR CA  
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.  
Double bond geometry as shown.

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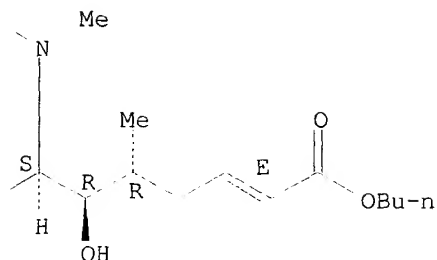


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1 REFERENCES IN FILE CA (1962 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 14 OF 17 REGISTRY COPYRIGHT 2002 ACS  
 RN **457612-98-5** REGISTRY  
 CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, ethyl ester (9CI) (CA INDEX NAME)  
 FS PROTEIN SEQUENCE; STEREOSEARCH  
 SQL **11**  
 NTE cyclic  
 modified (modifications unspecified)

type	-----	location	-----	description
uncommon	Aaa-1	-	-	
uncommon	Abu-2	-	-	
uncommon	Sar-3	-	-	
stereo	Ala-8	-	D	

SEQ 1 XXXLVLAALL V

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

MF C64 H113 N11 O14

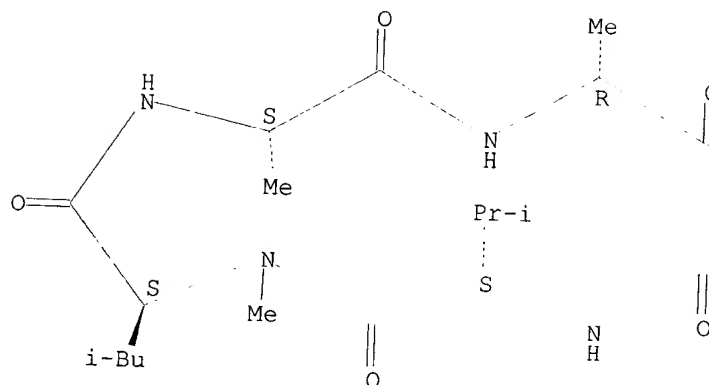
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LC STN Files: CA, CAPLUS, USPATFULL

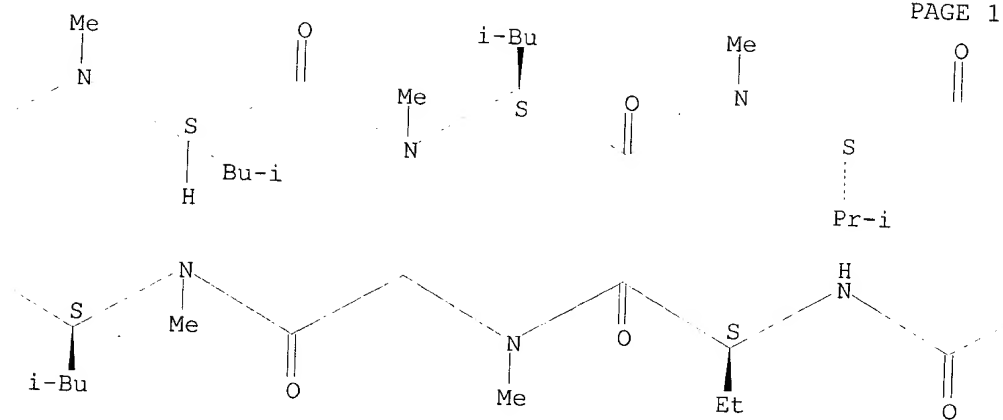
Absolute stereochemistry.

Double bond geometry as shown.

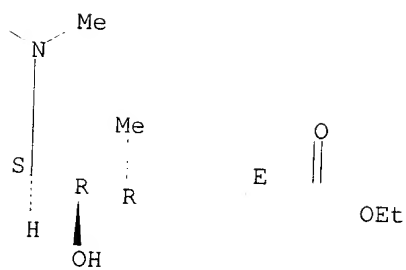
PAGE 1-A



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PAGE 1-C



1 REFERENCES IN FILE CA (1962 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER: 15 OF 17 REGISTRY COPYRIGHT 2002 ACS

RN 122547-85-7 REGISTRY

CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, methyl ester (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 1,4,7,10,13,16,19,22,25,28,31-Undecaazacyclotritriacontane, cyclic peptide deriv.

CN Cyclosporin A, 6-[(3R,4R)-6,7-didehydro-3-hydroxy-8-methoxy-N,4-dimethyl-8-oxo-L-2-aminooctanoic acid]-

FS PROTEIN SEQUENCE; STEREOSEARCH

SQL 11

NTE cyclic

modified (modifications unspecified)

type	location			description
uncommon	Aaa-1	-	-	
uncommon	Abu-2	-	-	
uncommon	Sar-3	-	-	
stereo	Ala-8	-	D	

SEQ 1 XXXLVLAALL V

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

MF C63 H111 N11 O14

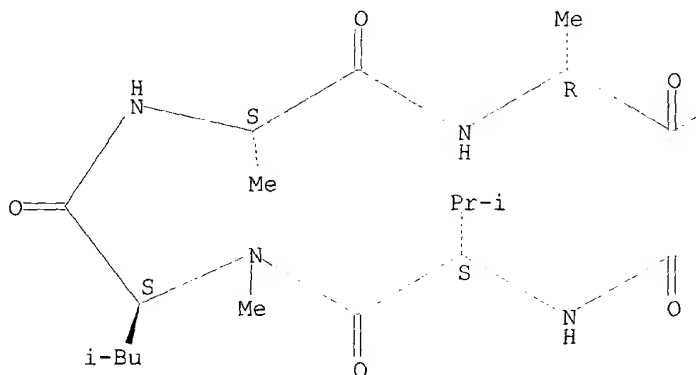
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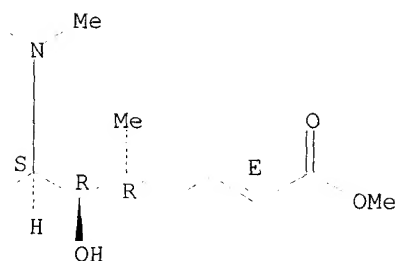
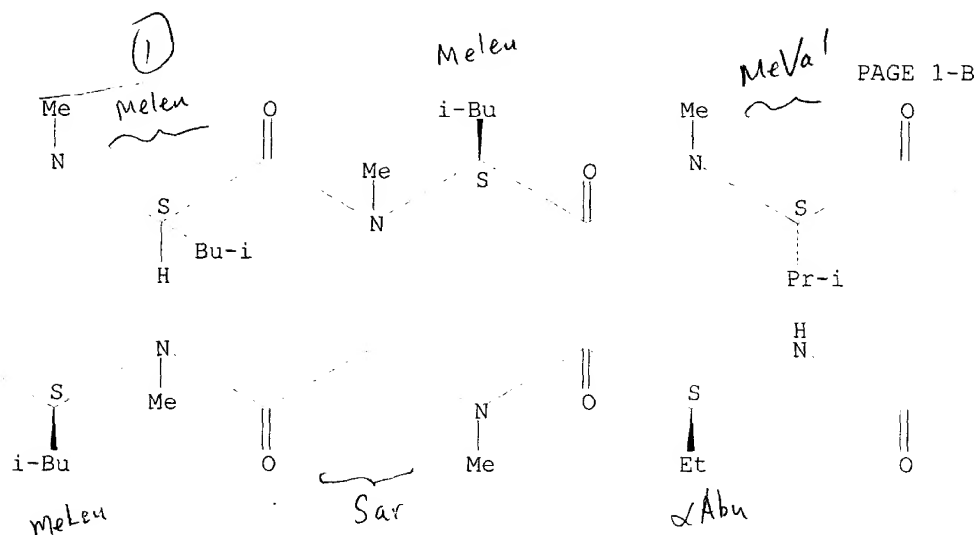
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

Double bond geometry as shown.

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2 REFERENCES IN FILE CA (1962 TO DATE)  
2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

REFERENCE 2: 111:127017

L8 ANSWER 16 OF 17 REGISTRY COPYRIGHT 2002 ACS

RN 100364-58-7 REGISTRY

CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 1,4,7,10,13,16,19,22,25,28,31-Undecaazacyclotritriacontane, cyclic peptide deriv.

CN Cyclosporin A, 6-[(3R,4R,6E)-6,7-didehydro-3-hydroxy-N,4-dimethyl-L-2-aminooctanedioic acid]-

OTHER NAMES:

CN AM 1A

CN Cyclosporin A metabolite 203-218

CN M 203-218

FS PROTEIN SEQUENCE; STEREOSEARCH

SQL 11

NTE cyclic

modified (modifications unspecified)

type	----- location -----	description
uncommon	Aaa-1	-
uncommon	Abu-2	-
uncommon	Sar-3	-
stereo	Ala-8	D

SEQ 1 XXXLVLAALL V

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

DR 122547-86-8

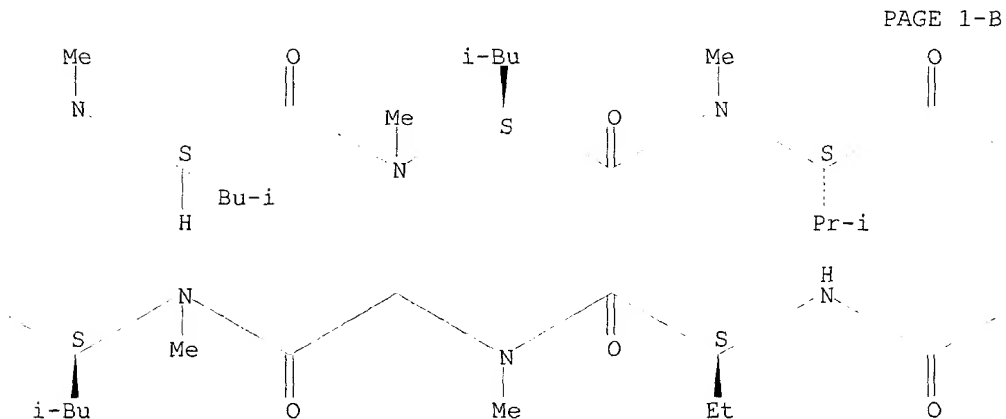
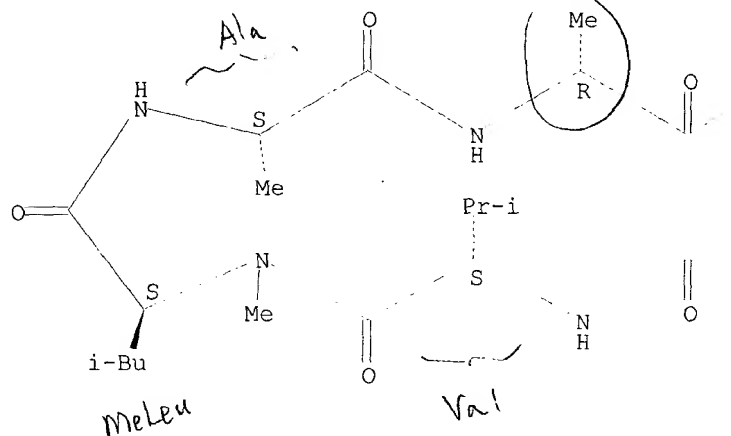
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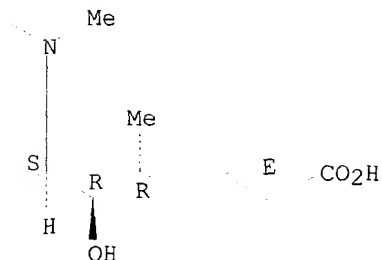
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.

Double bond geometry as shown.



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 25 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601  
 REFERENCE 2: 135:86519  
 REFERENCE 3: 124:306383  
 REFERENCE 4: 117:83083  
 REFERENCE 5: 116:15264  
 REFERENCE 6: 115:270244  
 REFERENCE 7: 115:269869  
 REFERENCE 8: 115:149642  
 REFERENCE 9: 115:105665  
 REFERENCE 10: 115:64248

L8 ANSWER 17 OF 17 REGISTRY COPYRIGHT 2002 ACS

RN **59865-13-3** REGISTRY

CN Cyclosporin A (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 1,4,7,10,13,16,19,22,25,28,31-Undecaazacyclotritriacontane, cyclic peptide deriv.

OTHER NAMES:

CN 7: PN: WO0002548 PAGE: 30 claimed protein

CN Antibiotic S 7481F1

CN Ciclosporin

CN Cipol N

CN Consupren

CN Cyclosporin

CN Cyclosporine

CN Cyclosporine A

CN Cyclo[L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-(3R,4R,6E)-6,7-didehydro-3-hydroxy-N,4-dimethyl-L-2-aminooctanoyl-L-2-aminobutanoyl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl]

CN Neoplanta

CN Neoral

CN OL 27-400

CN Ramihyphin A

CN S-Neoral  
 CN Sandimmun  
 CN Sandimmun Neoral  
 CN Sandimmune  
 CN Sang-35  
 CN SangCyA  
 CN SDZ-OXL 400  
 FS PROTEIN SEQUENCE; STEREOSEARCH  
 SQL 11  
 NTE cyclic  
 modified (modifications unspecified)

type	location			description
uncommon	Aaa-1	-	-	
uncommon	Abu-2	-	-	
uncommon	Sar-3	-	-	
stereo	Ala-8	-	D	

## PATENT ANNOTATIONS (PNTE):

Sequence | Patent

Source | Reference

=====+=====

Not Given|WO2000002548

|claimed PAGE

|30

SEQ 1 XXXLVLAALL V

## \*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

DR 56645-58-0, 55126-45-9, 104250-72-8, 223528-56-1

MF C62 H111 N11 O12

CI COM

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN\*, BIOBUSINESS, BIOSIS,  
 BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS,  
 CHEMLIST, CIN, CSCHM, CSNB, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU,  
 DRUGUPDATES, EMBASE, HSDB\*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK\*,  
 MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PHARMASEARCH, PROMT, RTECS\*,  
 TOXCENTER, USAN, USPAT2, USPATFULL, VETU

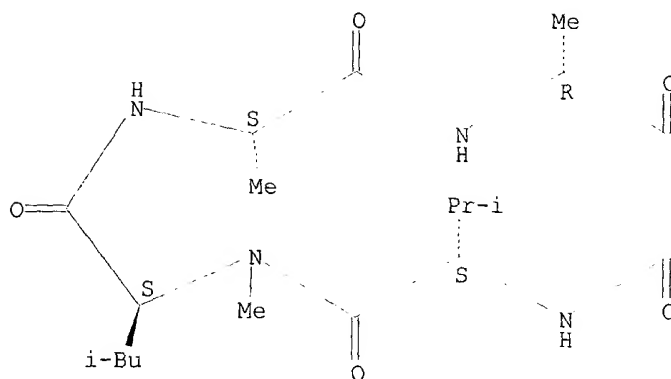
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Other Sources: WHO

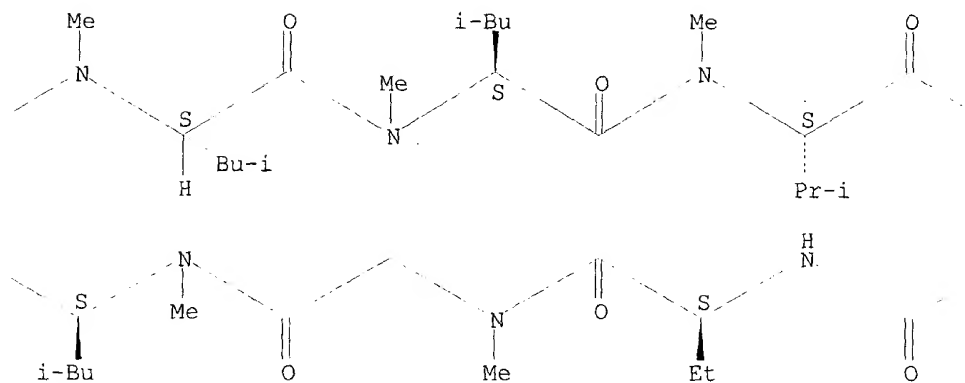
Absolute stereochemistry.

Double bond geometry as shown.

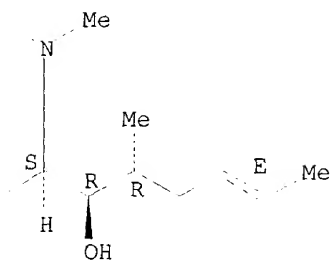
PAGE 1-A



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11693 REFERENCES IN FILE CA (1962 TO DATE)  
 297 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 11721 REFERENCES IN FILE CAPLUS (1962 TO DATE)



REFERENCE 1: 137:358273  
REFERENCE 2: 137:358158  
REFERENCE 3: 137:357970  
REFERENCE 4: 137:352901  
REFERENCE 5: 137:351400  
REFERENCE 6: 137:351382  
REFERENCE 7: 137:351341  
REFERENCE 8: 137:351074  
REFERENCE 9: 137:349850  
REFERENCE 10: 137:348601

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 15:34:49 ON 12 DEC 2002  
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FILE COVERS 1907 - 12 Dec 2002 VOL 137 ISS 24  
FILE LAST UPDATED: 11 Dec 2002 (20021211/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

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L44 ANSWER 1 OF 29 HCAPLUS COPYRIGHT 2002 ACS  
AN ~~2002:695724~~ HCAPLUS  
DN 137:226601  
TI Cyclosporins for the treatment of respiratory diseases  
IN Or, Yat Sun; Lazarova, Tsvetelina; Hamann, Blake  
Christopher  
PA Enanta Pharmaceuticals, Inc., USA  
SO PCT Int. Appl., 29 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
IC ICM A61K

CC 1-7 (Pharmacology)

Section cross-reference(s): 34, 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002069902	A2	20020912	WO 2002-US6541	20020305 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2002142946	A1	20021003	US 2001-800856	20010305 <--
PRAI	US 2001-800856	A	20010305 <--		
OS	MARPAT 137:226601				
AB	Novel semisynthetic cyclosporin analogs contg. different amino acids are synthesized for use as pharmaceuticals. The compds. can be used for the treatment of asthma, allergic rhinitis, bronchitis, etc. Thus, cyclosporin analogs were prepd. and their immunosuppressant activity was detd. by using the inhibition of the phosphate activity as the parameter.				
ST	cyclosporin analog topical respiratory disease prepn				
IT	Catalysts				
	(Nolan's; cyclosporins for the treatment of respiratory diseases)				
IT	Nose				
	(allergic rhinitis; cyclosporins for the treatment of respiratory diseases)				
IT	Bronchi				
	(bronchitis; cyclosporins for the treatment of respiratory diseases)				
IT	Bronchi				
	(chronic bronchitis; cyclosporins for the treatment of respiratory diseases)				
IT	Lung, disease				
	(chronic obstructive; cyclosporins for the treatment of respiratory diseases)				
IT	Anti-inflammatory agents				
	Asthma				
	Cystic fibrosis				
	Immunosuppressants				
	Lymphocyte				
	(cyclosporins for the treatment of respiratory diseases)				
IT	Respiratory tract				
	(disease; cyclosporins for the treatment of respiratory diseases)				
IT	Drug delivery systems				
	(inhalants; cyclosporins for the treatment of respiratory diseases)				
IT	Drug delivery systems				
	(topical; cyclosporins for the treatment of respiratory diseases)				
IT	172222-30-9, Grubbs' ruthenium catalyst 223415-64-3				
	RL: CAT (Catalyst use); USES (Uses)				
	(cyclosporins for the treatment of respiratory diseases)				
IT	100364-58-7P 457612-98-5P 457612-99-6P				
	457613-00-2P 457613-01-3P 457613-02-4P				
	457613-03-5P 457613-04-6P 457613-05-7P				
	457613-06-8P 457613-07-9P 457613-08-0P				
	457613-09-1P 457613-10-4P 457613-11-5P				
	RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)				
	(cyclosporins for the treatment of respiratory diseases)				
IT	96-33-3, Methyl acrylate 624-48-6, Methyl maleate				
	RL: RCT (Reactant); RACT (Reactant or reagent)				

(cyclosporins for the treatment of respiratory diseases)  
IT **122547-85-7P**  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(cyclosporins for the treatment of respiratory diseases)  
IT 59865-13-3, Cyclosporin A  
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT  
(Reactant or reagent); USES (Uses)  
(cyclosporins for the treatment of respiratory diseases)

L44 ANSWER 2 OF 29 HCAPLUS COPYRIGHT 2002 ACS  
AN 2002:365395 HCAPLUS  
DN 137:105954  
TI Synthesis of Cyclosporin A-Derived Affinity Reagents by Olefin Metathesis  
AU Smulik, Jason A.; Diver, Steven T.; Pan, Fan; Liu, Jun O.  
CS Department of Chemistry, University at Buffalo the State University of New  
York, Amherst, NY, 14260, USA  
SO Organic Letters (2002), 4(12), 2051-2054  
CODEN: ORLEF7; ISSN: 1523-7060  
PB American Chemical Society  
DT Journal  
LA English  
CC 9-14 (Biochemical Methods)  
Section cross-reference(s): 28  
AB New affinity reagents were synthesized using alkene metathesis to directly  
modify the MeBmt side chain of cyclosporin A. The reagents were used to  
detect novel cyclophilins from cellular exts.  
ST cyclosporin A affinity reagent prepn olefin metathesis  
IT Alkenes, biological studies  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(metathesis; synthesis of cyclosporin A-derived affinity reagents by  
olefin metathesis)  
IT Organic synthesis  
(synthesis of cyclosporin A-derived affinity reagents by olefin  
metathesis)  
IT Cyclophilins  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(synthesis of cyclosporin A-derived affinity reagents by olefin  
metathesis)  
IT 406502-99-6  
RL: CAT (Catalyst use); USES (Uses)  
(synthesis of cyclosporin A-derived affinity reagents by olefin  
metathesis)  
IT 59865-13-3, Cyclosporin A  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(synthesis of cyclosporin A-derived affinity reagents by olefin  
metathesis)  
IT **442912-25-6P** 442912-26-7P 442912-27-8P 442912-28-9P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(synthesis of cyclosporin A-derived affinity reagents by olefin  
metathesis)  
IT 9012-36-6P, Sepharose  
RL: RGT (Reagent); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(synthesis of cyclosporin A-derived affinity reagents by olefin  
metathesis)

RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD  
RE  
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L44 ANSWER 3 OF 29 HCAPLUS COPYRIGHT 2002 ACS

AN 2001:262803 HCAPLUS

DN 135:86519

TI Cyclosporin A metabolism in brown bullhead, *Ameriurus nebulosus*

AU Jegorov, A.; Halada, P.; Safarcik, K.

CS Galena a.s., Ceske Budejovice, 370 05, Czech Rep.

SO Fish Physiology and Biochemistry (2001), Volume Date 2000, 23(3), 257-264

CODEN: FPBIEP; ISSN: 0920-1742

PB Kluwer Academic Publishers

DT Journal

LA English

CC 1-2 (Pharmacology)

Section cross-reference(s): 12

AB Fungi suggested to be used in the control of mosquito larvae produce biol. active cyclopeptides - cyclosporins, which can potentially accumulate in the fish feeding the infected larvae. Whereas toxicity of cyclosporins was obsd. at the higher doses in man and various exptl. animals, the fish tolerated surprisingly high cyclosporin blood levels. Hydroxycyclosporins predominated among metabolites excreted into water. In contrast, various N-demethylated cyclosporins created the major part of metabolites identified in the liver and bile. Two new metabolites are described - AM1N and AM6N,10N, which were not so far reported from mammals. Due to the much higher tolerance to cyclosporin, brown bullhead can serve the exptl. model to obtain cyclosporin metabolites.

ST bullhead *Ameriurus cyclosporine* metab

IT *Ictalurus nebulosus*

(cyclosporin A metab. in brown bullhead, *Ameriurus nebulosus*)

IT 59865-13-3, Cyclosporin A

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(cyclosporin A metab. in brown bullhead, *Ameriurus nebulosus*)

IT 89270-23-5 89270-25-7 89270-26-8 89270-28-0 100364-58-7  
348084-97-9 348085-00-7

RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)

(cyclosporin A metab. in brown bullhead, *Ameriurus nebulosus*)

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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- L44 ANSWER 4 OF 29 HCAPLUS COPYRIGHT 2002 ACS  
AN 1998:743427 HCAPLUS  
DN 130:119267  
TI Isolation, identification and immunosuppressive activity of a new IMM-125 metabolite from human liver microsomes. Identification of its cyclophilin A-IMM-125 metabolite complex by nanospray tandem mass spectrometry  
AU Lhoest, G. J. J.; De Jong, A. P. J. M.; Meiring, H. D.; Maton, N.; Latinne, D.; Verbeeck, R. K.; Otte, J. B.; Zurini, M.  
CS Department of Pharmaceutical Sciences-UCL, Pharmacokinetics and Metabolism Unit, FATC Laboratory of Mass Spectrometry, Brussels, B-1200, Belg.  
SO Journal of Mass Spectrometry (1998), 33(10), 936-942  
CODEN: JMSPFJ; ISSN: 1076-5174  
PB John Wiley & Sons Ltd.  
DT Journal  
LA English  
CC 1-7 (Pharmacology)  
AB The isolation from human liver microsomes and identification by electrospray mass spectrometry and tandem mass spectrometry of a new metabolite of IMM-125 resulting from the biotransformation of the amino acid 1 vinylic Me group to a carboxylic acid, called the IMM-125-COOH metabolite, is described. It was found that the complex of this new metabolite with cyclophilin A is formed less easily than the corresponding cyclophilin A-IMM-125-CH2OH main metabolite and cyclophilin A-IMM-125 complexes. However, when formed, the IMM-125-COOH metabolite-cyclophilin A complex requires more collision-induced dissocn. (CID) to dissoc. the complex than the complexes formed with the two other ligands. The nanospray tandem mass spectrum of the IMM-125-COOH metabolite-cyclophilin A complex (m/z 1755) gives rise to cyclophilin A-ligand complexes of m/z 1751 by elimination of CO2 and of m/z 1749 by loss of CO2 and H2O or glycerol. Since immunosuppressive activity is known to be dependent on the formation of a binary complex between cyclophilin A and the drug and since the target for the binary complex was found to be the calcium- and calmodulin-dependent protein phosphatase, calcineurin, it could be interesting to measure for structurally related immunosuppressive drugs the CID energy necessary to dissoc. the binary complexes in order to evaluate whether a correlation with the phosphatase activity could be

derived.

ST IMM125 metabolite liver microsome immunosuppressant

IT Cyclophilins  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(A; isolation, identification and immunosuppressive activity of IMM-125 metabolite from human liver microsomes)

IT Immunosuppressants  
Liver  
Microsome  
(isolation, identification and immunosuppressive activity of IMM-125 metabolite from human liver microsomes)

IT 9025-75-6, Calcineurin  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(inhibition of; isolation, identification and immunosuppressive activity of IMM-125 metabolite from human liver microsomes)

IT 219740-62-2P  
RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MFM (Metabolic formation); PUR (Purification or recovery); ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation)  
(isolation, identification and immunosuppressive activity of IMM-125 metabolite from human liver microsomes)

IT 135548-15-1, IMM 125  
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(isolation, identification and immunosuppressive activity of IMM-125 metabolite from human liver microsomes)

IT 162936-12-1  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)  
(isolation, identification and immunosuppressive activity of IMM-125 metabolite from human liver microsomes)

RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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L44 ANSWER 5 OF 29 HCAPLUS COPYRIGHT 2002 ACS

AN 1996:306593 HCAPLUS

DN 125:6043

TI Controlling protein association and subcellular localization with a synthetic ligand that induces heterodimerization of proteins

AU Belshaw, Peter J.; Ho, Steffan N.; Crabtree, Gerald R.; Schreiber, Stuart L.

CS Howard Hughes Medical Institute, Harvard University, Cambridge, MA, 02138, USA

- SO Proceedings of the National Academy of Sciences of the United States of America (1996), 93(10), 4604-4607  
CODEN: PNASA6; ISSN: 0027-8424
- PB National Academy of Sciences
- DT Journal
- LA English
- CC 13-1 (Mammalian Biochemistry)
- AB Extracellular growth and differentiation factors induce changes in gene expression in the nucleus by initiating a series of protein assocns. that alter the subcellular localization of intracellular signaling proteins. Initial events involve receptor homo- or heterodimerization and subsequent recruitment of cytosolic signaling proteins to the inner leaflet of the plasma membrane. Intermediate events involve the translocation of proteins into the nucleus. Late events involve the recruitment of transcriptional activators to the vicinity of specific genes in the nucleus, resulting in increased gene transcription. The ability to induce signals at each of these three phases of signaling pathways is illustrated by the use of a heterodimeric chem. inducer of dimerization that causes a proximal relation between two different target proteins.
- ST protein heterodimerization ligand synthesis
- IT Proteins, specific or class, biological studies  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(GF3'; controlling protein assocn. and subcellular localization with a synthetic ligand that induces heterodimerization of proteins)
- IT Proteins, specific or class, biological studies  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(JC3E; controlling protein assocn. and subcellular localization with a synthetic ligand that induces heterodimerization of proteins)
- IT Molecular association  
Signal transduction, biological  
(controlling protein assocn. and subcellular localization with a synthetic ligand that induces heterodimerization of proteins)
- IT Proteins, specific or class  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(FA, controlling protein assocn. and subcellular localization with a synthetic ligand that induces heterodimerization of proteins)
- IT 177080-80-7P  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
(synthesis if FKCsA, a ligand which induces heterodimerization of proteins)
- IT 138957-22-9 177080-79-4  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(synthesis if FKCsA, a ligand which induces heterodimerization of proteins)
- IT 162926-18-3P 177080-78-3P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(synthesis if FKCsA, a ligand which induces heterodimerization of proteins)
- L44 ANSWER 6 OF 29 HCAPLUS COPYRIGHT 2002 ACS
- AN 1996:156367 HCAPLUS
- DN 124:306383
- TI A rifampicin-induced hepatic microsomal enzyme system for the generation of cyclosporine metabolites
- AU Tamolang, M. B.; Liu, W. T.; Pang, H.; Ren, Ying; Wong, P. Y.
- CS Department of Clinical Biochemistry, University of Toronto, Toronto, ON, Can.

- SO Pharmacological Research (1995), 32(3), 141-8  
CODEN: PHMREP; ISSN: 1043-6618
- PB Academic
- DT Journal
- LA English
- CC 1-2 (Pharmacology)
- Section cross-reference(s): 9
- AB A drug-induced rabbit hepatic microsomal enzyme system has been developed to produce milligram quantities of cyclosporine metabolites (CMs). Using a rifampicin-induced microsomal prepn. in the presence of a NADPH regenerating system, 60% of the cyclosporine (CsA) was converted to CMs in 2 h. The CMs were recovered by solid phase extrn., and sepd. by gradient high performance liq. chromatog. with two Ultrasphere Ocy1 (C8) columns connected in tandem. More than 20 CMs were resolved. The quantities of major CMs produced by 45 mg of microsomal proteins were established by comparing peak areas with known concns. of authentic CM stds. These major CMs included AM1, AM9, AM19, AM4N, AM1c and the aldehydic isomers (AM1cAL plus AM1AL). Other CMs that were not quantified included AM14N, AM4N9, AM1A, AM1c9, and AM1D1. Several CMs remained to be identified. All CMs were detected by RIA using a non-specific CsA antiserum. The purity of the CMs were confirmed by fast at. bombardment mass spectrometry. Similar findings were obsd. when erythromycin or troleandomycin was used to induce the hepatic microsomal enzymes. The procedure used to generate CMs was simple. With the enzyme fraction derived from one rabbit liver, 90 to 100 mg of CMs can be obtained. In this study, the metabolite patterns of CsA produced by rabbit liver microsomes were shown to resemble those obsd. for humans. These results indicate the possibility of using rabbit models to predict CsA biotransformation in man. The CMs generated by this enzyme system can be used to acquire information relevant to the situation in man.
- ST cyclosporine metabolite generation liver microsome enzyme;  
biotransformation cyclosporine liver microsome enzyme
- IT Drug biotransformation  
(rabbit model for prediction of biotransformation in humans; use of a rifampicin-induced hepatic microsomal enzyme system for generation of cyclosporine metabolites)
- IT Immunosuppressants  
Liver  
Microsome  
(use of a rifampicin-induced hepatic microsomal enzyme system for generation of cyclosporine metabolites)
- IT 9035-51-2, Cytochrome P 450, biological studies  
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); CAT (Catalyst use); BIOL (Biological study); PROC (Process); USES (Uses)  
(IIIA; use of a rifampicin-induced hepatic microsomal enzyme system for generation of cyclosporine metabolites)
- IT 114-07-8, Erythromycin 2751-09-9, Troleandomycin 13292-46-1, Rifampicin  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)  
(use of a rifampicin-induced hepatic microsomal enzyme system for generation of cyclosporine metabolites)
- IT 59865-13-3DP, Cyclosporine, metabolites 89270-23-5P, AM 4N 89270-25-7P, AM 9 89270-26-8P, AM 19 89270-28-0P, AM 1 89270-29-1P, AM 1c 100364-58-7P, AM 1A 107335-27-3P, AM 14N 107335-28-4P, AM 1c9 112077-93-7P, AM 4N9 121886-75-7P, AM 1D1 176365-87-0P, AM 1AL 176365-88-1P, AM 1cAL  
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); MFM (Metabolic formation); PUR (Purification or recovery); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation)  
(use of a rifampicin-induced hepatic microsomal enzyme system for



generation of cyclosporine metabolites)  
IT 59865-13-3, Cyclosporine  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL  
(Biological study); PROC (Process)  
(use of a rifampicin-induced hepatic microsomal enzyme system for  
generation of cyclosporine metabolites)

L44 ANSWER 7 OF 29 HCAPLUS COPYRIGHT 2002 ACS  
AN 1992:483083 HCAPLUS  
DN 117:83083  
TI The synergistic immunosuppressive potential of cyclosporin metabolite  
combinations  
AU Radeke, Heinfried H.; Christians, Uwe; Sewing, Karl F.; Resch, Klaus  
CS Inst. Molekularpharmakol., Med. Hochsch., Hannover, D-3000/61, Germany  
SO International Journal of Immunopharmacology (1992), 14(4),  
595-604  
CODEN: IJIMDS; ISSN: 0192-0561  
DT Journal  
LA English  
CC 1-7 (Pharmacology)  
AB Of the 29 cyclosporin (CS) metabolites defined so far, 7 representatives  
were isolated from the bile of liver grafted patients, purified by HPLC,  
and characterized by FAB-MS and/or 1H-NMR. These were used to det. the  
growth inhibitory effects on Con A-stimulated rat lymph node (LN)  
lymphocytes. Metabolites dild. in culture medium at concns. rechecked by  
HPLC at the resp. assay time were added and proliferation detd. by  
[3H]thymidine incorporation after 48 h. A 50% growth inhibition of LN by  
single metabolites (AM) was achieved at the following concns. (mg/L): CS,  
0.023; primary metabolites AM1, 0.11; AM1c, 0.65; AM9, 1.05; secondary  
metabolites AM19, 1.02; AM4N9, 1.02; H355, 1.85; and AM1A, 4.5. Although  
all metabolites were immunosuppressive at higher concns. in vitro on a  
single metabolite level, only AM1, with 20% of the activity of native CS,  
seemed to play a role in vivo. However, when the antiproliferative  
effects were tested on double or triple metabolite combinations, a strong  
synergism was found not only of primary metabolites, but even with  
combinations including secondary metabolites. The concn. of the  
participating metabolites necessary to decrease LN growth by 50% was far  
below the trough levels obsd. in vivo. Finally, to mimic to some extent  
the in vivo situation, the interaction of native CS with single  
metabolites or double combinations was studied. In contrast to the clear  
synergism in the absence of CS, the combinations of metabolites with  
native CS resulted in an additive growth inhibition. These results  
indicate an immunosuppressive potential of all metabolites tested and a  
clear synergism of metabolites in the absence of CS. Although up to  
double metabolite combinations did only additively enhance CS-induced  
immunosuppression, the combination of 29 metabolites occurring in vivo  
might have significant immunosuppressive effects in situations where CS  
levels drop below active concns.

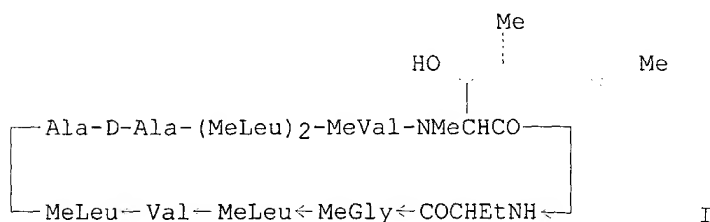
ST cyclosporin metabolite immunosuppression synergism  
IT Immunosuppressants  
(cyclosporin and metabolites, synergistic potential of)  
IT Lymphocyte  
(cyclosporin metabolite synergistic immunosuppressive potential on)  
IT Drug interactions  
(synergistic, of cyclosporin and metabolites, on immunosuppression)

IT 59865-13-3, Cyclosporin 89270-25-7 89270-26-8 89270-28-0  
89270-29-1 100364-58-7 112077-93-7 142785-21-5, Cyclosporin  
A metabolite H 355  
RL: BIOL (Biological study)  
(immunosuppressive activity of, cyclosporin metabolite combinations  
synergistic effects on)

IT 59865-13-3D, Cyclosporin, metabolites  
RL: PRP (Properties)

(synergistic immunosuppressive potential of)

L44 ANSWER 8 OF 29 HCAPLUS COPYRIGHT 2002 ACS  
 AN 1992:15264 HCAPLUS  
 DN 116:15264  
 TI Investigations on the metabolic pathways of cyclosporine: I. Excretion of cyclosporine and its metabolites in human bile - isolation of 12 new cyclosporine metabolites  
 AU Christians, U.; Strohmeyer, S.; Kownatzki, R.; Schiebel, H. M.; Bleck, J.; Greipel, J.; Kohlhaw, K.; Schottmann, R.; Sewing, K. F.  
 CS Inst. Allg. Pharmakol., Med. Hochsch. Hannover, Hannover, Germany  
 SO Xenobiotica (1991), 21(9), 1185-98  
 CODEN: XENOBH; ISSN: 0049-8254  
 DT Journal  
 LA English  
 CC 1-2 (Pharmacology)  
 GI



AB Cyclosporine (I) metabolites of known and unknown structures were isolated by semipreparative HPLC from human bile from the T-tube of liver-grafted patients who received cyclosporine treatment. Their structures were elucidated by FAB mass spectrometry and 1H-NMR spectroscopy. Twelve of the cyclosporine metabolites, with known chem. structures, were isolated and identified using authentic std. material. Four isolated fractions contained trihydroxylated metabolites; two fractions contained dihydroxylated, demethylated, metabolites; one fraction contained a trihydroxylated, demethylated metabolite; and one fraction a monohydroxylated, demethylated metabolite. The exact metab. sites were partially defined. Two carboxylated cyclosporine metabolites, of which one was hydroxylated in an unknown position, were isolated. One new metabolite proved to be a glucuronylated phase II metabolite. Deglucuronylation of this metabolite by .beta.-glucuronidase yielded metabolite AM1c. The proposed structure was AM1c-glucuronide; is a proposed extension of the Hawk's Cay nomenclature of the cyclosporine metabolites for glucuronylated metabolites. One of the unknown metabolites was hydroxylated in two positions of amino acid 1. The proposed nomenclature was 'AM1ld', where 'ld' indicates hydroxylation of the .delta.C of amino acid 1. A metabolite with an aldehyde functional group at amino acid 1, which had two isomeric forms, was isolated. I.r.-spectroscopy indicated that isomerism may be caused by conjugation of the aldehyde group with the double bond between C6 and C7 of amino acid 1.

ST cyclosporine metab bile  
 IT Bile

(cyclosporine and its metabolites of human)  
 IT 89270-23-5 89270-24-6 89270-25-7 89270-26-8 89270-27-9  
 89270-28-0 89270-29-1 89288-32-4 100364-58-7 107335-27-3  
 107335-28-4 112077-93-7 129843-36-3 137459-34-8 137459-35-9  
 137459-36-0 137483-88-6 137483-89-7 137500-55-1 137500-58-4  
 137500-59-5

RL: BIOL (Biological study)  
 (as cyclosporine metabolite, in bile of humans)

- IT 59865-13-3, Cyclosporine  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(metab. of, in humans, metabolites in bile in)
- L44 ANSWER 9 OF 29 HCAPLUS COPYRIGHT 2002 ACS  
AN 1991:670244 HCAPLUS  
DN 115:270244  
TI Synergistic and antagonistic effects of combinations of cyclosporine A and its metabolites on inhibition of phytohemagglutinin-induced lymphocyte transformation in vitro  
AU Schultz, John C.; Lensmeyer, Gary L.; Wendal, Thad D.; Shahidi, Nasrollah T.; Wiebe, Donald A.; Carlson, Ian H.  
CS Div. Pediatr. Hematol./Oncol., Univ. Wisconsin, Madison, WI, 53792, USA  
SO Biochemical Pharmacology (1991), 42(7), 1403-10  
CODEN: BCPA6; ISSN: 0006-2952  
DT Journal  
LA English  
CC 1-7 (Pharmacology)  
AB Cyclosporine A (CsA) and purified CsA metabolites were tested alone and in combinations in cell cultures to det. their effects on PHA-induced human lymphocyte proliferation. CsA was more inhibitory than its metabolites at all concns. tested (0-1000 ng/mL). CsA exerted a max. inhibition (70% decrease in [Me-3H]thymidine incorporation) at concns.  $\geq$  300 ng/mL; metabolites M1, M17, and M21 depressed the response 46, 39, and 23%, resp., at 300 ng/mL. Metabolites M8, M18, M26, M25, M13, and M203-218 were noninhibitory. When combinations of M17 and CsA were tested, a synergistic effect occurred at combinations of low concns. of M17 and CsA and an antagonistic effect at higher concns. Of the 49 combinations of CsA and M17 tested, 30 were antagonistic, 16 synergistic, and 3 undecided (approaching additivism). When 49 combinations of CsA and the non-immunosuppressive metabolite M8 were tested, 29 combinations were synergistic, 17 antagonistic, 1 additive, and 2 undecided. Of the 29 synergistic combinations, 14 were strongly synergistic. The importance of interactions of CsA and its metabolites to the immunopharmacol. of CsA therapy is discussed.  
ST cyclosporine metabolite interaction lymphocyte immunosuppression  
IT Immunosuppressants  
(cyclosporin A and metabolites as, in lymphocytes of human, interactions in)  
IT Lymphocyte  
(cyclosporin A and metabolites immunosuppression of human, interactions in)  
IT Drug interactions  
(of cyclosporin A, with metabolites, lymphocyte immunosuppression response to, in human)  
IT 59865-13-3D, Cyclosporin A, derivs. 89270-23-5 89270-25-7 89270-26-8  
89270-28-0 89270-29-1 100364-58-7 107335-27-3 107335-28-4  
RL: BIOL (Biological study)  
(immunosuppressant effects of cyclosporin A and metabolite, interactions in)  
IT 59865-13-3, Cyclosporin A  
RL: PRP (Properties)  
(interaction of, with metabolites, lymphocyte immunosuppression response to, in human)
- L44 ANSWER 10 OF 29 HCAPLUS COPYRIGHT 2002 ACS  
AN 1991:669869 HCAPLUS  
DN 115:269869  
TI Investigations on the metabolic pathways of cyclosporine: II.  
Elucidation of the metabolic pathways in vitro by human liver microsomes  
AU Christians, U.; Strohmeyer, S.; Kownatzki, R.; Schiebel, H. M.; Bleck, J.; Kohlhaw, K.; Schottmann, R.; Sewing, K. F.

CS Inst. Allg. Pharmakol., Med. Hochsch. Hannover, Hannover, Germany  
SO Xenobiotica (1991), 21(9), 1199-210  
CODEN: XENOBH; ISSN: 0049-8254  
DT Journal  
LA English  
CC 1-2 (Pharmacology)  
AB Cyclosporine and its metabolites, isolated from human bile and identified by FAB mass spectrometry and 1H-NMR spectroscopy, were metabolized by human liver microsomes for the identification of new cyclosporine metabolites. From these data a metabolic pathway for cyclosporine, which includes these new cyclosporine metabolites, has been proposed. The new metabolites were isolated by semipreparative HPLC and their chem. structures were elucidated by FAB mass spectrometry. These isolated metabolites were further metabolized and the products identified by FAB mass spectrometry. Fourteen metabolites, whose structure has not yet been elucidated, were isolated after metab. of structurally identified cyclosporine metabolites, and chem. structures for five of these metabolites were proposed. The structures of the new cyclosporine metabolites were: (i) a N-demethylated, carboxylated deriv. (AM1A4N), (ii) a di-hydroxylated, N-demethylated deriv. (AM14N9), (iii) a hydroxylated and carboxylated deriv. (AM1A9), (iv) a dihydroxylated, cyclized and N-demethylated deriv. (AM1c4N9) and (v) a cyclized and carboxylated (AM1cA) deriv. A proposed cyclosporine metabolic pathway comprises a total of 29 metabolites. It consists of four main branches originating from metabolites AM1, AM1c, AM9, and AM4N.  
ST cyclosporine metab liver microsome  
IT Microsome  
(cyclosporine metab. by human liver)  
IT Liver, metabolism  
(cyclosporine metab. by microsomes of human)  
IT 89270-23-5 89270-25-7 89270-26-8 89270-27-9 89270-28-0  
89270-29-1 89288-32-4 100364-58-7 107335-28-4 112077-93-7,  
Cyclosporin A metabolite 4N9 119386-81-1, Cyclosporin A metabolite 14N9  
129843-36-3, Cyclosporin A metabolite 1AL 137500-55-1, Cyclosporin A  
metabolite 1ld 137500-56-2, Cyclosporin A metabolite 1A4N 137500-57-3,  
Cyclosporin A metabolite 1A9 137500-58-4, Cyclosporin A metabolite 1Ac  
137500-59-5 137500-60-8, Cyclosporin A metabolite 1c4N9  
RL: BIOL (Biological study)  
(as cyclosporine metabolite, in liver microsomes of humans)  
IT 59865-13-3, Cyclosporine  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL  
(Biological study); PROC (Process)  
(metab. of, by liver microsomes of humans)  
L44 ANSWER 11 OF 29 HCAPLUS COPYRIGHT 2002 ACS  
AN 1991:549642 HCAPLUS  
DN 115:149642  
TI Micro-quantification of cyclosporine and its metabolites and determination  
of their spectral absorptivities  
AU Fu, Irong; Bowers, Larry D.  
CS Dep. Lab. Med. Pathol., Univ. Minnesota, Minneapolis, MN, 55455, USA  
SO Clinical Chemistry (Washington, DC, United States) (1991),  
37(7), 1185-90  
CODEN: CLCHAU; ISSN: 0009-9147  
DT Journal  
LA English  
CC 1-1 (Pharmacology)  
AB A micromethod for the anal. of cyclosporine (CsA), based on quantification of its constituent amino acids is reported. The amino acids were released by gas-phase hydrolysis, derivatized with fluorenylmethyl chloroformate, and sepd. and analyzed in a reversed-phase HPLC system. The imprecision (CV) of the amino acid anal. was <4%, and several detns. of the amt. of std. CsA were within 1% of the weighed material. The detection limits

(signal-to-noise ratio = 2) were 500 fmol for UV detection and 100 fmol for fluorescence detection. This method was also used to det. the UV absorptivities of CsA and five metabolites at 210, 214, and 230 nm. The molar absorptivity of most metabolites was about 10% higher than that of CsA, although the metabolite that was oxidized to a carboxyl group on the terminal carbon of N-methylbutenylmethylthreonine (AM1A) had a molar absorptivity about 40% higher than that of CsA.

ST cyclosporine metabolite detn HPLC fluorometry; liq chromatog cyclosporine metabolite

IT Spectrochemical analysis  
(UV, in cyclosporine and its metabolites detn.)

IT Spectrochemical analysis  
(fluorometric, in cyclosporine and its metabolites detn.)

IT Chromatography, column and liquid  
(high-performance, reversed-phase, in cyclosporine and its metabolites detn.)

IT 89270-23-5 89270-25-7 89270-26-8 89270-28-0 100364-58-7  
RL: ANT (Analyte); ANST (Analytical study)  
(detn. of, as cyclosporine metabolite, by HPLC)

IT 59865-13-3, Cyclosporine  
RL: ANT (Analyte); ANST (Analytical study)  
(detn. of, by HPLC, metab. in relation to)

L44 ANSWER 12 OF 29 HCAPLUS COPYRIGHT 2002 ACS

AN 1991:505665 HCAPLUS

DN 115:105665

TI Assessment of the biological activity of cyclosporine metabolites using the human JURKAT cell line

AU Freed, B. M.; Stevens, C.; Brooks, C.; Cramer, S.; Lempert, N.; Rosano, T. G.

CS Dep. Surg., Albany Med. Coll., Albany, NY, 12208, USA

SO Transplantation Proceedings (1991), 23(1, Bk. 2), 980-1  
CODEN: TRPPA8; ISSN: 0041-1345

DT Journal

LA English

CC 1-7 (Pharmacology)

AB In the human leukemia T-cell line JURKAT 6.8, the most potent of the cyclosporine metabolites had approx. 10% of the immunosuppressive activity of the parent compds., whereas the other metabolites were less potent or inactive. The results highlight the need to assess the effects of the metabolites in vivo.

ST cyclosporine metabolite immunosuppressant T lymphocyte

IT Immunosuppressants  
(cyclosporine and its metabolites as, in T-lymphocytes of humans)

IT Lymphocyte  
(T-, cyclosporine and its metabolites immunosuppressant activity in human)

IT 89270-25-7 89270-26-8 89270-28-0 89270-29-1 100364-58-7  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(immunosuppressant activity of, as cyclosporine metabolite, in T-lymphocytes of humans)

IT 59865-13-3D, Cyclosporine, metabolites  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(immunosuppressant activity of, in T-lymphocytes of humans)

IT 59865-13-3, Cyclosporine  
RL: BIOL (Biological study)  
(immunosuppression from, in T-lymphocytes of humans, metabolites in)

L44 ANSWER 13 OF 29 HCAPLUS COPYRIGHT 2002 ACS

AN 1991:464248 HCAPLUS  
 DN 115:64248  
 TI Additive and synergistic effects of cyclosporine metabolites on glomerular mesangial cells  
 AU Radeke, Heinfried H.; Christians, Uwe; Bleck, Joerg S.; Sewing, Karl F.; Resch, Klaus  
 CS Abt. Molekularpharmakol., Med. Hochsch., Hannover, D-3000/61, Germany  
 SO Kidney International (1991), 39(6), 1255-66  
 CODEN: KDYIA5; ISSN: 0085-2538  
 DT Journal  
 LA English  
 CC 1-7 (Pharmacology)  
 AB Out of the 29 cyclosporine (Cs) metabolites defined so far, 10 representative ones were isolated from bile of liver grafted patients, purified by HPLC, and their structure specified by FAB-MS and 1H NMR. These were used to det. the growth inhibitory effects on Sprague Dawley rat glomerular mesangial cells (MC). Metabolite dilns. were added to cultured MC for 72 h and [3H]thymidine incorporation was measured. A 50% growth inhibition by single metabolites (M) on MC was achieved at the following concns. (mg/L): Cs: 1.25; M21: 6.0; M18: 9.0; M26: 10.5; M1: 10.8; M8: 10.8; M17: 12.5; M13: >20.0; M25: >25.0; M203-218: >50.0; H355: >50.0. The activity was correlated to the degree of metabolization as the group of six "active" compds. included 4 primary metabolites (hydroxylated or demethylated derivs. of Cs: M21, M18, M1, M17), whereas the 4 "inactive" compds. exclusively were secondary metabolites (demethylated, hydroxylated and/or oxidized primary metabolites: M13, M25, M203-218, H355). Combinations of active metabolites with or without Cs resulted in an additive antiproliferative effect. Although single metabolite activities are not relevant in vivo, already combinations of 3 (M1 + M17 + M18) or 4 metabolites (M17 + M18 + M21 + H355) resulted in a significant growth inhibition at concns. of the participating metabolites measured in urine of liver transplanted patients. Moreover, significant synergistic activities were detd. with combinations including secondary metabolites. A final set of expts. discharged unspecific cytotoxic effects. The inhibition of MC [3H]thymidine incorporation was completely reversible and moreover, direct mesangiolysis was excluded for both single and combined metabolite actions. Thus, considering rat MC proliferation as an initial kidney cell model system for subsequent, more detailed studies measuring functional parameters, it was demonstrated that activities of single metabolites are related to their chem. structure. More importantly, mimicking to some extent the patients' situation, combinations of metabolites at concns. occurring in vivo reduced MC proliferation in culture in an at least additive fashion, suggesting that side effects of Cs treatment might be attributed to combined Cs metabolite actions.

ST cyclosporin A metabolite kidney mesangium toxicity  
 IT Kidney, toxic chemical and physical damage  
 (mesangium, cyclosporin A metabolites toxicity to, additive and synergistic effects in)  
 IT 89270-23-5P 89270-25-7P 89270-26-8P 89270-28-0P 89270-29-1P  
 100364-58-7P 107335-27-3P 107335-28-4P 135125-20-1P  
 135160-89-3P  
 RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)  
 (prepn. and toxicity of, as cyclosporin A metabolite to glomerular mesangial cells)  
 IT 59865-13-3, Cyclosporin A  
 RL: PRP (Properties)  
 (toxicity of, to glomerular mesangial cells)  
 IT 59865-13-3D, Cyclosporin A, metabolites  
 RL: PRP (Properties)  
 (toxicity of, to glomerular mesangial cells, additive and synergistic effects in)

AN 1990:565083 HCAPLUS  
 DN 113:165083  
 TI Biologic activity of cyclosporine metabolites  
 AU Sewing, K. F.; Christians, U.; Kohlhaw, K.; Radeke, H.; Strohmeyer, S.;  
 Kownatzki, R.; Budniak, J.; Schottmann, R.; Bleck, J. S.; et al.  
 CS Abt. Allg. Pharmakol., Med. Hochsch., Hannover, D-3000/61, Germany  
 SO Transplantation Proceedings (1990), 22(3), 1129-34  
 CODEN: TRPPA8; ISSN: 0041-1345  
 DT Journal  
 LA English  
 CC 1-7 (Pharmacology)  
 AB The authors studied nephrotoxicity of cyclosporine (CyA) and its  
 metabolites in liver graft patients. There were no differences in  
 patients with or without CyA nephrotoxicity with respect to CyA doses,  
 coadministered nephrotoxic drugs, liver parameters, kidney function before  
 transplantation, and CyA trough levels in blood. The only independent  
 variable in this study influencing CyA nephrotoxicity was the CyA  
 metabolite pattern. There was a high correlation between CyA  
 nephrotoxicity and the double hydroxylated CyA metabolites, esp. with the  
 double hydroxylated and cyclized metabolite H270(26), but not with CyA  
 itself. The CyA metabolite toxicity detected seemed to be the result of a  
 characteristic cytochrome P 450 isoenzyme pattern of patients developing  
 CyA nephrotoxicity. The alteration of the CyA metabolite pattern by  
 rejection or cholestasis resulted in an increase in concn. of the  
 metabolites H250(8) and H350(203-218) in blood and urine. The other  
 metabolites were not affected. The metabolite pattern is similar during  
 acute rejection and cholestasis. It is different from that characteristic  
 of for CyA metabolite toxicity since there is no increase in cyclized  
 metabolites. Both metabolite patterns have an elevated concn. of  
 metabolite H240(8) in common. It is possible that metabolite H250(8) is  
 directly cyclized to metabolite H270(26). Whether this is of clin.  
 importance remains to be evaluated.  
 ST cyclosporine metabolite kidney toxicity  
 IT Kidney, toxic chemical and physical damage  
 (cyclosporine toxicity to, metabolites in, in liver transplantation in  
 humans)  
 IT Transplant and Transplantation, animal  
 (of liver, cyclosporine metab. and kidney toxicity in, in humans)  
 IT Liver  
 (transplant, cyclosporine metab. and kidney toxicity in, in humans)  
 IT 89270-23-5 89270-24-6 89270-25-7 89270-26-8 89270-27-9  
 89270-28-0 89270-29-1 89288-32-4 100364-58-7 107335-27-3  
 107335-28-4 129843-36-3  
 RL: BIOL (Biological study)  
 (as cyclosporine metabolite, kidney toxicity in relation to, in liver  
 transplantation in humans)  
 IT 59865-13-3D, Cyclosporin A, metabolites  
 RL: FORM (Formation, nonpreparative)  
 (formation of, kidney toxicity in relation to, in liver transplantation  
 in humans)  
 IT 59865-13-3, Cyclosporine  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL  
 (Biological study); PROC (Process)  
 (metab. of, kidney toxicity and pharmacol. in human in relation to, in  
 liver transplants.)

L44 ANSWER 15 OF 29 HCAPLUS COPYRIGHT 2002 ACS  
 AN 1990:545029 HCAPLUS  
 DN 113:145029  
 TI Sandimmun metabolites: their potential to cause adverse reactions in the  
 rat  
 AU Donatsch, P.; Rickenbacher U.; Ryffel, B.; Brouillard, J. F.  
 CS Dep. Drug Saf. Assess., Sandoz, Basel, CH-4002, Switz.

- SO Transplantation Proceedings (1990), 22(3), 1137-40  
CODEN: TRPPA8; ISSN: 0041-1345
- DT Journal
- LA English
- CC 1-7 (Pharmacology)
- AB The toxic effects of Sandimmun cyclosporin (CyA) and its 4 metabolites were studied in spontaneously hypertensive rats. The metabolites 17, 18, 21, and 203-318 had no nephrotoxic and/or hepatotoxic potential. There was no evidence of immunosuppressive activity of the 4 metabolites. The exposure of the animals to the various compds. expressed as area under the curve value or mean plasma level differed markedly, being highest for CyA and 203-318, followed by metabolites 18, 17, and 21.
- ST Sandimmun metabolite toxicity liver kidney; cyclosporin A metabolite toxicity liver kidney
- IT Kidney, toxic chemical and physical damage  
Liver, toxic chemical and physical damage  
(cyclosporin A metabolites toxicity to)
- IT 89270-23-5, Cyclosporin A metabolite 21 89270-28-0, Cyclosporin A metabolite 17 89270-29-1, Cyclosporin A metabolite 18  
**100364-58-7**, Cyclosporin A metabolite 203-218  
RL: PRP (Properties)  
(toxicity of, to kidney and liver)
- IT 59865-13-3, Cyclosporin A  
RL: PRP (Properties)  
(toxicity of, to kidney and liver, metabolites in relation to)
- L44 ANSWER 16 OF 29 HCAPLUS COPYRIGHT 2002 ACS
- AN 1990:526201 HCAPLUS
- DN 113:126201
- TI Studies on the biologic activities of Sandimmun metabolites in humans and in animal models: review and original experiments
- AU Fahr, A.; Hiestand, P.; Byffel, B.
- CS Dep. Pharmacol. Dev. Preclin. Res., Sandoz Pharm. Ltd., Basel, Switz.
- SO Transplantation Proceedings (1990), 22(3), 1116-24  
CODEN: TRPPA8; ISSN: 0041-1345
- DT Journal; General Review
- LA English
- CC 1-7 (Pharmacology)
- AB Expts. from the authors' lab. on information on the immunosuppressive activity of cyclosporin A (CyA) metabolites are described. An overview of the available information about the immunosuppressive activity of CyA metabolites is given.
- ST Sandimmun metabolite pharmacol; review cyclosporine metabolite pharmacol
- IT Immunosuppressants  
(cyclosporine and metabolites as, in humans and lab. animals)
- IT 89270-23-5 89270-28-0 89270-29-1 **100364-58-7**  
RL: BIOL (Biological study)  
(as cyclosporine metabolite, immunosuppressive activity and pharmacol. of, in humans and lab. animals)
- IT 59865-13-3, Cyclosporin A  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(metab. and immunosuppressive activity of, in humans and lab. animals)
- L44 ANSWER 17 OF 29 HCAPLUS COPYRIGHT 2002 ACS
- AN 1990:91112 HCAPLUS
- DN 112:91112
- TI Three commercial polyclonal immunoassays for cyclosporin A in whole blood compared: 2. Cross-reactivity of the antisera with cyclosporin A metabolites
- AU Lensmeyer, Gary L.; Wiebe, Donald A.; Carlson, Ian H.; DeVos, Diane J.
- CS Dep. Pathol. Lab. Med., Univ. Wisconsin, Madison, WI, 53792, USA
- SO Clinical Chemistry (Washington, DC, United States) (1990),



36(1), 119-23

CODEN: CLCHAU; ISSN: 0009-9147

DT Journal

LA English

CC 1-1 (Pharmacology)

AB The authors demonstrate the diverse selectivity of three com. polyclonal "cyclosporine" immunoassays for cyclosporin A (CsA) metabolites by comparing anal. responses of nine metabolites added to drug-free whole-blood specimens (range 0 to 2000 .mu.g/L) and assayed by the Abbott TDx fluorescence polarization immunoassay (FPIA), the Incstar Cyclo-Trac RIA (RIA), and the Sandoz RIA. Cross-reactivity-defined as the relative response (slope of regression line) of metabolite/parent CsA over the assay's linear range of concns.-differed for each metabolite among the three assays. Overall, Abbott's antiserum exhibited the greatest affinity for the metabolites, the Sandoz antiserum the least. Ranges of cross-reactivity for the metabolites over all three assays were M1 (14-44%), M8 (9-20%), M13 (13-26%), M17 (50-116%), M18 (17-79%), M21 (4-54%), M25 (<1-52%), M26 (<1-29%), and M203-218 (7-51%). The specificities of the Abbott, Incstar, and Sandoz polyclonal assays thus differ significantly, and this brings into question the practical utility of comparing data generated for patients' specimens by different procedures.

ST cyclosporin A metabolite blood polyclonal immunoassay  
IT Antiserums

(to cyclosporin A, in polyclonal immunoassays, cross-reactivity with cyclosporin A metabolites of)  
IT Immunochemical analysis

(immunoassay, polyclonal, cyclosporin A metabolites detn. in human blood by three, comparison of, cross-reactivity of antiserum in relation to)

IT 59865-13-3D, Cyclosporin A, metabolites  
RL: ANT (Analyte); ANST (Analytical study)  
(detn. of, in human blood by three polyclonal immunoassays, cross-reactivity of antiserum in)

IT 89270-23-5, Cyclosporin A metabolite 21 89270-25-7, Cyclosporin A metabolite 1 89270-26-8, Cyclosporin A metabolite 8 89270-28-0, Cyclosporin A metabolite 17 89270-29-1, Cyclosporin A metabolite 18 100364-58-7, Cyclosporin A metabolite 203-218 107335-27-3, Cyclosporin A metabolite 25 107335-28-4, Cyclosporin A metabolite 26  
RL: ANT (Analyte); ANST (Analytical study)  
(detn. of, in human blood by three polyclonal immunoassays, cross-reactivity of antiserum with cyclosporin A metabolites in)

L44 ANSWER 18 OF 29 HCAPLUS COPYRIGHT 2002 ACS  
AN 1989:546244 HCAPLUS

DN 111:146244

TI Urinary excretion of cyclosporin and 17 of its metabolites in renal allograft recipients

AU Bleck, J. S.; Schlitt, H. J.; Christians, U.; Thiesemann, C.; Strohmeyer, S.; Schottmann, R.; Kohlhaw, K.; Wonigeit, K.; Sewing, K. F.  
CS Abt. Allg. Pharmakol., Med. Hochsch. Hannover, Hannover, D-3000/61, Fed. Rep. Ger.

SO Pharmacology (1989), 39(3), 160-4  
CODEN: PHMGBN; ISSN: 0031-7012

DT Journal

LA English

CC 1-2 (Pharmacology)

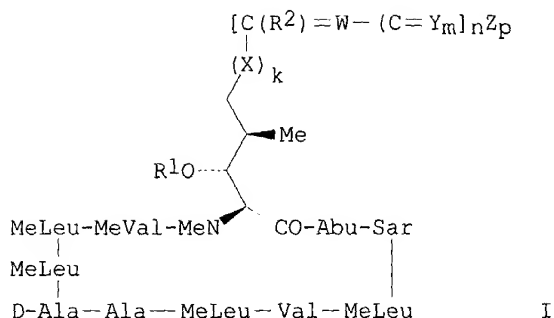
AB Renal elimination of the immunosuppressant cyclosporin is virtually unknown. Therefore, in renal allograft recipients under steady-state conditions, the urinary excretion of cyclosporin and 17 of its metabolites in blood and 24-h urine was studied. Cyclosporin and its metabolites were measured by HPLC. Metabolite but not cyclosporin excretion was strongly correlated with creatinine clearance. Metabolites 18 and 26

(.beta.,.epsilon.-cyclic metabolite) were rarely found in blood but were excreted in considerable amts. in urine. Approx. 3% of the administered dose of cyclosporin per day underwent renal elimination in unchanged form or as metabolites. There is glomerular filtration of cyclosporin metabolites, a difference in the rate of elimination between cyclosporin and the metabolites, and some kind of metab. or active transport mechanism for metabolites in the kidney.

ST cyclosporin metabolite urine excretion  
 IT Urine  
     (cyclosporine and metabolites excretion in human)  
 IT Blood  
     (cyclosporine and metabolites of human)  
 IT 89270-23-5, Cyclosporin A metabolite 21 89270-24-6, Cyclosporin A metabolite 9 89270-25-7, Cyclosporin A metabolite 1 89270-26-8, Cyclosporin A metabolite 8 89270-28-0, Cyclosporin A metabolite 17 89270-29-1, Cyclosporin A metabolite 18 89288-32-4, Cyclosporin A metabolite 10 100364-58-7, Cyclosporin A metabolite 203-218 107335-27-3, Cyclosporin A metabolite 25 107335-28-4, Cyclosporin A metabolite 26  
 RL: BIOL (Biological study)  
     (formation of and urinary excretion of, as cyclosporine metabolite, in humans)  
 IT 59865-13-3, Cyclosporin A  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
     (metab. and urinary excretion of, in humans)  
 IT 59865-13-3D, Cyclosporin A, metabolites  
 RL: PROC (Process)  
     (urinary excretion of, in humans)

L44 ANSWER 19 OF 29 HCAPLUS COPYRIGHT 2002 ACS  
 AN 1989:527017 HCAPLUS  
 DN 111:127017  
 TI Fluorescence polarization immunoassay for cyclosporin A and metabolites based on novel cyclosporin A derivatives  
 IN Wang, Nai Yi; Wang, Philip P.; Morrison, Marjorie Anne  
 PA Abbott Laboratories, USA  
 SO Eur. Pat. Appl., 17 pp.  
 CODEN: EPXXDW  
 DT Patent  
 LA English  
 IC ICM C07K007-64  
 ICS G01N033-68; G01N033-58  
 CC 1-1 (Pharmacology)  
 Section cross-reference(s): 26  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 283801	A2	19880928	EP 1988-103397	19880304 <--
	EP 283801	A3	19900530		
	R: BE, CH, DE, ES, FR, GB, IT, LI				
	JP 63258491	A2	19881025	JP 1988-73057	19880325 <--
	US 5239057	A	19930824	US 1991-776890	19911015 <--
	US 5427960	A	19950627	US 1994-318570	19941005 <--
PRAI	US 1987-31494		19870327	<--	
	US 1989-376244		19890706	<--	
	US 1991-776890		19911015	<--	
	US 1993-60598		19930512	<--	
OS	MARPAT 111:127017				
GI					



AB A method is described for prepn. of cyclosporin A derivs. I [k = 0-1 (k = 0 only if n = 1); m = 0-2; n, p = 0-1; R<sup>1</sup> = H or a protecting group; R<sup>2</sup> = H, lower alkyl, or CH(OH)Me; W = 1-20 (not including H) atoms of C, N, O, S, with .ltoreq.2 heteroatoms bonded together and with O never bonded to O or S; X = CH<sub>2</sub>, CHOH, C(O) (n = 0), or CH<sub>2</sub>OH (p = 0); Y = O, S, or NH; Z = a poly(amino acid), a poly(amino acid) deriv., a fluorescent moiety, OH, NH<sub>2</sub>, NHH<sub>2</sub>, ORa, SRa, NHRa, NRaRb (Ra, Rb = stable C1-10 chain), SH, or a leaving group; MeVal, MeLeu, Sar, and Abu represent residues of N-methylvaline, N-methyleucine, sarcosine, and L-.alpha.-aminobutyric acid, resp.]. The derivs. are used as (1) immunogens in formation of antibodies specific to cyclosporin A and some metabolites, and (2) precursors in synthesis of fluorescent tracers having .gtoreq.1 epitope in common with cyclosporin A and some metabolites. Antibodies and tracers are employed in a fluorescence polarization immunoassay (FPIA) for cyclosporin A and metabolites in biol. fluids. [6-(Carboxymethyloximino)-3-(R)-hydroxy-4-(R)-methyl-2-(S)-methylaminohexanoyl]6cyclosporin A (I; k = 0; m, n, p = 1; R<sup>1</sup>, R<sup>2</sup> = H; W = NOCH<sub>2</sub>; Y = O; Z = OH) (prepn. given) was conjugated to bovine serum albumin with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide-HCl, and the resulting immunogen was used to immunize exptl. animals. A fluorescent cyclosporin A tracer was prepd. from [7-carboxy-3-(R)-hydroxy-4-(R)-methyl-2-(S)-methylamino-6-heptenoyl]6cyclosporin A (I; k = 0; m, n, p = 1; R<sup>2</sup> = H; W = CH; Y = O; Z = OH) and aminomethylfluorescein-HCl. To serum or plasma samples was added pptn. reagent (30 mM NH<sub>4</sub>OAc in 98.5% aq. Me<sub>2</sub>CHOH). Following mixing and centrifuging, samples were analyzed with an automated assay employing an Abbott TDx Analyzer and a Cyclosporin and Metabolites Reagent pack. FPIA sensitivity was 15 ng/mL for cyclosporin A and metabolites. In a comparison of 208 clin. samples against an available RIA, linear regression anal. gave a slope of 1.153, an intercept of 21.06, and a correlation coeff. of 0.813.

ST cyclosporin A deriv fluorescence polarization immunoassay

IT Proteins, properties

RL: PRP (Properties)

(pptn. of, with ammonium acetate and isopropanol)

IT Antibodies

RL: BIOL (Biological study)

(to cyclosporin A and metabolites, for fluorescence-polarization immunoassay)

IT Albumins, compounds

RL: BIOL (Biological study)

(conjugates, with cyclosporin A derivs., for antibody prodn.)

IT 122547-75-5

RL: PRP (Properties)

(conjugation of, with albumin)

IT 59865-13-3, Cyclosporin A 59865-13-3D, Cyclosporin A, metabolites

RL: ANT (Analyte); ANST (Analytical study)

(detn. of, by fluorescence polarization immunoassay)

IT 83602-41-9  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(oxidn. of, with osmium tetroxide and periodate in albumin-cyclosporin  
A deriv. conjugate prepn.)

IT 122547-79-9P  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. and conjugation with albumin)

IT 122575-49-9P  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of, for fluorescence polarization immunoassay for cyclosporin  
A)

IT 121584-52-9P 122547-77-7P 122547-78-8P 122547-80-2P 122547-81-3P  
122547-82-4P 122547-83-5P  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of, in albumin-cyclosporin A deriv. conjugate prepn.)

IT 122547-84-6P **122547-85-7P 122547-86-8P**  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of, in cyclosporin A-aminomethylfluorescein conjugate prepn.)

IT 67-63-0, Isopropanol, biological studies  
RL: BIOL (Biological study)  
(protein pptn. with ammonium acetate and)

IT 631-61-8, Ammonium acetate  
RL: BIOL (Biological study)  
(protein pptn. with isopropanol and)

IT 122547-74-4  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(reaction of, in prepn. of albumin-cyclosporin A deriv. conjugate)

IT 2921-14-4, Carboxymethoxylamine hemihydrochloride 122547-87-9  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(reaction of, with cyclosporin A deriv.)

L44 ANSWER 20 OF 29 HCAPLUS COPYRIGHT 2002 ACS  
AN 1989:450102 HCAPLUS  
DN 111:50102  
TI Comparison of the in vitro immunosuppressive effects of cyclosporin A and  
its metabolites  
AU Copeland, K. R.; Yatscoff, R. W.; Rush, D.; Jeffery, J. R.  
CS Dep. Clin. Chem., Health Sci. Clin. Res. Cent., Winnipeg, MB, R3A 1R9,  
Can.  
SO Transplantation Proceedings (1989), 21(1, Book 2), 1449-52  
CODEN: TRPPA8; ISSN: 0041-1345  
DT Journal  
LA English  
CC 1-7 (Pharmacology)

AB Five cyclosporin A (I) metabolites were isolated from I-treated kidney and  
liver transplant patients' urine and bile, resp., and tested for their  
immunosuppressive activity singly as well as in combination with I. A  
mixed lymphocyte system was used to test the immunosuppressant activity.  
All the 5 metabolites (M-17, M-18, M-8, M-26, and M-203-218) exhibited  
immunosuppressant activity, but at a significantly lower level than that  
by I... M-17, the major metabolite found in human blood, was .apprx.10%  
as active as I. Additive, but not synergistic, effects were obsd. when  
these metabolites were combined with I. The metabolites were isolated by  
using semipreparative HPLC and their structure confirmed by mass and NMR  
spectroscopy.

ST immunosuppression cyclosporin A metabolite

IT Immunosuppressants  
(cyclosporin A and metabolites as)

IT Lymphocyte  
(cyclosporin A and metabolites effect on human, immunosuppression in  
relation to)

IT 89270-26-8 89270-28-0, M17 89270-29-1, M-18 **100364-58-7**  
107335-28-4, M 26

- RL: BIOL (Biological study)  
(cyclosporin A metabolite, immunosuppressant activity of, in human lymphocytes)
- IT 59865-13-3, Cyclosporin A  
RL: BIOL (Biological study)  
(immunosuppression by, in human lymphocytes, metabolites in relation to)
- L44 ANSWER 21 OF 29 HCAPLUS COPYRIGHT 2002 ACS  
AN 1989:107532 HCAPLUS  
DN 110:107532  
TI Distribution of cyclosporin A metabolites among plasma and cells in whole blood: effect of temperature, hematocrit, and metabolite concentration  
AU Lensmeyer, Gary L.; Wiebe, Donald A.; Carlson, Ian H.  
CS Dep. Pathol., Univ. Wisconsin Hosp., Madison, WI, 53792, USA  
SO Clinical Chemistry (Washington, DC, United States) (1989), 35(1), 56-63  
CODEN: CLCHAU; ISSN: 0009-9147  
DT Journal  
LA English  
CC 1-2 (Pharmacology)  
AB Drug-free whole-blood samples supplemented with the cyclosporins and samples from transplant patients receiving cyclosporin A (CsA) were equilibrated at 4, 22, and 37.degree. for 2.5 h; the plasma and cells were sepd., and the fractions were assayed by HPLC. Partitioning of CsA and metabolites among plasma and cells was diverse and not always predictable in the patients' samples. Overall, although widely variable, >50% of the total concn. of metabolites M1, M8, M9, M10, M16, M17, U1, U8, and U9 in whole blood was assocd. with the cells, whereas >50% of M13, M18, M21, M25, M26, M203-218, U2, U3, U4, U5, and U7 was assocd. with plasma. A decrease in hematocrit from 47.8% to 24%, an increase of the sample's temp. (from 4 to 37.degree.), or an increase in analyte concn. (usually >500 .mu.g/L for selected metabolites) increased the relative portion assocd. with plasma in a nonlinear fashion. Parent CsA was most influenced by these changes; its relative concns. in plasma varied from 18% to 50%. These data support the preferential use of whole blood for therapeutic monitoring of cyclosporins.
- ST cyclosporin A metabolite distribution plasma cell  
IT Blood plasma  
(cyclosporin A metabolites in human)
- IT 59865-13-3, Cyclosporin A  
RL: PROC (Process)  
(distribution of, among blood plasma and cells in humans)
- IT 59865-13-3D, Cyclosporin A, metabolites  
RL: PROC (Process)  
(distribution of, among blood plasma and cells, in humans)
- IT 89270-23-5 89270-25-7 89270-26-8 89270-27-9 89270-28-0  
89270-29-1 89288-32-4 100364-58-7 107335-27-3 107335-28-4  
119386-81-1  
RL: PROC (Process)  
(distribution of, as cyclosporin A metabolite, among blood plasma and cells in humans)
- L44 ANSWER 22 OF 29 HCAPLUS COPYRIGHT 2002 ACS  
AN 1988:485582 HCAPLUS  
DN 109:85582  
TI Deposition of nine metabolites of cyclosporine in human tissues, bile, urine, and whole blood  
AU Lensmeyer, Gary L.; Wiebe, D. A.; Carlson, I. H.  
CS Dep. Pathol., Univ. Wisconsin Hosp., Madison, WI, USA  
SO Transplantation Proceedings (1988), 20(2, Suppl. 2), 614-22  
CODEN: TRPPA8; ISSN: 0041-1345  
DT Journal

LA English  
CC 1-1 (Pharmacology)  
AB Cyclosporine (CsA) and 9 metabolites were detd. in human bile, urine, blood, and tissues by HPLC with a Bond Elut cyanopropyl extn. cartridge, a Zorbax CN column, a mobile phase of H<sub>2</sub>O-MeCN-tetrahydrofuran-HOAc-n-butylamine (610:375:20:0.16:0.1), and detection of 214 nm. The coeff. of variance was <10% and the precision for CsA in fat was 7.2% at 2290 .mu.g/kg. Several of the metabolites were found at concns. exceeding those of CsA in bile, urine, blood, and most tissues, except fat and pancreas. The HPLC profiles for CsA and metabolites in urine and blood were different.

ST cyclosporine metabolite blood urine tissue HPLC; liq chromatog  
cyclosporine metabolite  
IT Bile  
Blood analysis  
Urine analysis  
(cyclosporine and metabolites detn. in human, by HPLC)

IT Adipose tissue, composition  
Brain, composition  
Kidney, composition  
Liver, composition  
Lung, composition  
Lymph gland  
Muscle, composition  
Pancreas, composition  
Spleen, composition  
(cyclosporine and metabolites of human, detn. of, by HPLC)

IT Chromatography, column and liquid  
(high-performance, cyclosporine and metabolites detn. by, in human tissues)

IT 59865-13-3 89270-25-7 89270-26-8 89270-28-0 89270-29-1  
100364-58-7 107335-27-3 107335-28-4  
RL: ANT (Analyte); ANST (Analytical study)  
(detn. of, as cyclosporine metabolite, in human tissues, by HPLC)

IT 59865-13-3, Cyclosporin A 59865-13-3D, Cyclosporin A, metabolites  
RL: ANT (Analyte); ANST (Analytical study)  
(detn. of, in human tissues, by HPLC)

L44 ANSWER 23 OF 29 HCAPLUS COPYRIGHT 2002 ACS  
AN 1988:485581 HCAPLUS  
DN 109:85581  
TI Measurement of cyclosporine and 18 metabolites in blood, bile, and urine by high-performance liquid chromatography  
AU Christians, U.; Schlitt, H. J.; Bleck, J. S.; Schiebel, H. M.; Kownatzki, R.; Maurer, G.; Strohmeyer, S. S.; Schottmann, R.; Wonigeit, K.; et al.  
CS Zent. Biochem., Med. Hochsch., Hannover, Fed. Rep. Ger.  
SO Transplantation Proceedings (1988), 20(2, Suppl. 2), 609-13  
CODEN: TRPPA8; ISSN: 0041-1345  
DT Journal  
LA English  
CC 1-1 (Pharmacology)  
AB Cyclosporine (CsA), 11 known metabolites, and 7 unknown metabolites were detd. in human blood, bile and urine by HPLC. The blood samples were treated with MeCN-H<sub>2</sub>O (pH 3.0), cyclosporin D was added as an internal std., and the compds. were extd. on a column contg. octyl sorbent with CH<sub>2</sub>Cl<sub>2</sub> as eluent. The CH<sub>2</sub>Cl<sub>2</sub> was evapd. and the compds. were reconstituted in a mobile phase of MeCN-H<sub>2</sub>O (pH 3.0) (50:50). For urine samples, the internal std. and 250 .mu.L MeCN were added per mL of urine followed by the same extn. procedure. Bile, 500 mL, was mixed with CH<sub>2</sub>Cl<sub>2</sub>, 500 mL, the CH<sub>2</sub>Cl<sub>2</sub> was evapd., and the residue was taken up into 150 mL MeCN-H<sub>2</sub>O and washed with hexane. Six mL of the aq. layer and 3 mL H<sub>2</sub>O were mixed and passed through the column. The CH<sub>2</sub>Cl<sub>2</sub> was evapd. and the residue was take up into the mobile phase as above. Three of the new

metabolites had immunosuppressive effects in mixed lymphocyte cultures and in anti-CD3-stimulated lymphocyte assays. None of the metabolites had nonspecific toxicity in Epstein-Barr virus-transformed B-cells.

ST immunosuppression cyclosporine metabolite; cyclosporine metabolite blood bile urine HPLC; liq chromatog cyclosporine metabolite

IT Bile  
Blood analysis  
Urine analysis  
(cyclosporine and metabolites detn. in human, by HPLC)

IT Immunosuppressants  
(cyclosporine metabolites)

IT Toxicity  
(of cyclosporine metabolites)

IT Chromatography, column and liquid  
(high-performance, cyclosporine and metabolites detn. by, in human bile and blood and urine)

IT 59865-13-3 89270-25-7 89270-26-8 89270-27-9 89270-28-0  
89270-29-1 89288-32-4 **100364-58-7** 107335-27-3 107335-28-4  
RL: ANT (Analyte); ANST (Analytical study)  
(detn. of, as cyclosporine metabolite, in human bile and blood and urine, by HPLC)

IT 59865-13-3, Cyclosporin A 59865-13-3D, Cyclosporin A, metabolites  
RL: ANT (Analyte); ANST (Analytical study)  
(detn. of, in human bile and blood and urine, by HPLC)

L44 ANSWER 24 OF 29 HCAPLUS COPYRIGHT 2002 ACS

AN 1988:142677 HCAPLUS

DN 108:142677

TI Liquid-chromatographic measurement of cyclosporin A and its metabolites in blood, bile, and urine

AU Christians, U.; Zimmer, K. O.; Wonigeit, K.; Maurer, G.; Sewing, K. F.

CS Abt. Allg. Pharmakol., Med. Hochsch. Hannover, Hannover, D-3000/61, Fed. Rep. Ger.

SO Clinical Chemistry (Washington, DC, United States) (1988), 34(1), 34-9  
CODEN: CLCHAU; ISSN: 0009-9147

DT Journal

LA English

CC 1-1 (Pharmacology)

AB Cyclosporin A and its metabolites were detd. in the blood, bile, and urine of humans by using solid-phase extn. columns and HPLC. To facilitate calcns. of concns. of cyclosporin A and its metabolites from the chromatograms, cyclosporin D was used as internal std. For the HPLC 2 sequential 250-mm anal. columns filled with reversed-phase octyl (C8) sorbent were used. Elution was done with a concave gradient of water, adjusted to pH 3.0 with H3PO4 and MeCN. Peaks were detected at 205 nm. For characterization of the chromatog. peaks, the authors isolated, by semi-preparative HPLC, 32 fractions representing peaks potentially related to cyclosporin A metabolites and reinjected them into the HPLC system under the same conditions as authentic cyclosporin A metabolites. Anal. recovery was 70-80%. The inter-assay coeffs. of variations for bile and urine were 7.2 and 12.3%, resp. The method was used for routine monitoring of cyclosporin A and its metabolites.

ST cyclosporin A metabolite detn HPLC; liq chromatog cyclosporin A metabolite; bile cyclosporin A metabolite HPLC; urine cyclosporin A metabolite HPLC; blood cyclosporin A metabolite HPLC

IT Bile  
Blood analysis  
Urine analysis  
(cyclosporin A and its metabolites detn. in human, by HPLC)

IT 89270-23-5 89270-24-6 89270-25-7 89270-26-8 89270-27-9  
89270-28-0 89270-29-1 89288-32-4 **100364-58-7** 107335-27-3  
107335-28-4

- RL: ANT (Analyte); ANST (Analytical study)  
(detn. of, in body fluid of humans, as cyclosporin A metabolite by HPLC)
- IT 59865-13-3, Cyclosporin A 59865-13-3D, Cyclosporin A, metabolites  
RL: ANT (Analyte); ANST (Analytical study)  
(detn. of, in body fluid of humans, by HPLC)
- L44 ANSWER 25 OF 29 HCAPLUS COPYRIGHT 2002 ACS  
AN 1988:15717 HCAPLUS  
DN 108:15717  
TI The in vitro activity, radioimmunoassay cross-reactivity, and molecular weight of thirteen rabbit cyclosporine metabolites  
AU Hartman, N. R.; Jardine, I.  
CS Dep. Pharmacol., Mayo Clin., Rochester, MN, 55905, USA  
SO Drug Metabolism and Disposition (1987), 15(5), 661-4  
CODEN: DMDSAI; ISSN: 0090-9556  
DT Journal  
LA English  
CC 1-2 (Pharmacology)  
AB Thirteen metabolites of cyclosporine were isolated from the bile of rabbits receiving i.v. cyclosporine. The mol. wts. of these metabolites were detd. by fast atom bombardment mass spectrometry. These mol. wts. were consistent with hydroxylated, N-demethylated, and carboxylated metabolites of cyclosporine as described previously. The in vitro activities of the metabolites were established using mitogen-stimulated lymphocyte proliferation assays. Only the two monohydroxylated metabolites were found to have significant activity, this being between 5 and 10% of that of the parent drug. The metabolites were also compared with cyclosporine in two com. radioimmunoassay kits. The metabolites were found to cross-react with the parent drug in amts. ranging 20-100%, with the least polar metabolites cross-reacting the most strongly. It is concluded that the cross-reacting metabolites measured by the presently available radioimmunoassays for cyclosporine probably do not represent significant addnl. immunosuppressive activity in vivo.
- ST cyclosporine metabolite mol wt immunosuppression; RIA cross reactivity cyclosporine metabolite
- IT Immunosuppression  
(by cyclosporine metabolites)
- IT Molecular weight  
(of cyclosporine metabolites)
- IT Immunochemical analysis  
(radioimmunoassay, cross reactivity, for cyclosporine metabolites and parent drug)
- IT 89270-25-7 89270-26-8 89270-28-0 100364-58-7 112077-93-7  
RL: PRP (Properties)  
(isolation and mol. wt. of, as cyclosporine metabolite, immunosuppressive activity and RIA cross-reactivity in)
- IT 59865-13-3D, Cyclosporine, metabolites  
RL: PRP (Properties)  
(isolation and mol. wt. of, immunosuppressive activity and RIA cross-reactivity in)
- L44 ANSWER 26 OF 29 HCAPLUS COPYRIGHT 2002 ACS  
AN 1988:15665 HCAPLUS  
DN 108:15665  
TI Identification and analysis of nine metabolites of cyclosporine in whole blood by liquid chromatography. 2: Comparison of patients' results  
AU Lensmeyer, Gary L.; Wiebe, Donald A.; Carlson, Ian H.  
CS Dep. Pathol. Lab. Med., Univ. Wisconsin, Madison, WI, 53792, USA  
SO Clinical Chemistry (Washington, DC, United States) (1987), 33(10), 1851-5  
CODEN: CLCHAU; ISSN: 0009-9147  
DT Journal



LA English  
CC 1-1 (Pharmacology)  
AB A HPLC assay [for parent cyclosporine (CsA) and nine metabolites] and a radioimmunoassay were used to detail the diversity of results among whole-blood samples from patients with transplanted organs. Results by HPLC vs RIA for CsA or for individual metabolites vs CsA (or RIA) were diverse, with correlation coeffs. (r) ranging from 0.058 to 0.933. RIA vs HPLC (sum of CsA + metabolites) gave the best comparison (slope = 0.931, yr-intercept 14 .mu.g/L, r = 0.933); but the scatter of data about the regression line remained significant (Sy/x = 132 .mu.g/L). Most important, RIA/HPLC(CsA) vs HPLC(sum of metabolites) was remarkably poor (r = 0.222). A 12-h pharmacokinetic curve (for drug concns. in a heart-transplant patient) displayed dissimilar times for peak concns. of CsA and metabolites; each differed in the proportion (48% to 81% of peak concn.) eliminated from blood over the 12 h. These studies exemplify the utility of a more-inclusive, specific assay to monitor the diverse disposition of cyclosporines in patients and to demonstrate the errors assocd. with use of the RIA/HPLC ratio technique to predict metabolite concns.

ST cyclosporine metabolite blood HPLC RIA; liq chromatog radioimmunoassay  
cyclosporine metabolite blood  
IT Blood analysis  
(cyclosporine and metabolites detn. in human, by HPLC vs. RIA)  
IT Chromatography, column and liquid  
(high-performance, cyclosporine and metabolites detn. in human blood by RIA vs.)  
IT Immunochemical analysis  
(radioimmunoassay, cyclosporine and metabolites detn. in human blood by HPLC vs.)  
IT 59865-13-3, Cyclosporin A 59865-13-3D, Cyclosporin A, metabolites  
89270-25-7 89270-26-8 89270-28-0 **100364-58-7**  
RL: ANT (Analyte); ANST (Analytical study)  
(detn. of, in human blood, by HPLC vs. RIA)

L44 ANSWER 27 OF 29 HCAPLUS COPYRIGHT 2002 ACS  
AN 1988:15664 HCAPLUS  
DN 108:15664  
TI Identification and analysis of nine metabolites of cyclosporine in whole blood by liquid chromatography. 1: Purification of analytical standards and optimization of the assay  
AU Lensmeyer, Gary L.; Wiebe, Donald A.; Carlson, Ian H.  
CS Dep. Pathol. Lab. Med., Univ. Wisconsin, Madison, WI, 53792, USA  
SO Clinical Chemistry (Washington, DC, United States) (1987),  
33(10), 1841-50  
CODEN: CLCHAU; ISSN: 0009-9147  
DT Journal  
LA English  
CC 1-1 (Pharmacology)  
AB An extn. and an isocratic HPLC sepn. of cyclosporine (CsA) and nine metabolites (M1, M8, M17, M18, M21, M25, M26, M203-218, and MUNDFl) from whole blood are described. Metabolites (for stds.) were purified from human bile with liq.-liq. and solid-phase extns., chromatographed on a cyanopropyl (CN) semipreparative HPLC column, and further purified on octyl, CN, and silica columns. The identity of each metabolite was verified with authentic stds. on three chem. different HPLC columns and on the basis of cross-reactivity data from radioimmunoassay. For the routine anal. method, 1 mL of whole blood is dild., hemolyzed, and applied to a Bond Elut CN (500 mg) cartridge to ext. CsA, metabolites, and cyclosporin C, the internal std. Interferences are removed by using four wash solns. and an addnl. cartridge of octyldecyl sorbent introduced prior to elution. Analytes are sepd. on a Zorbax CN anal. column maintained at 58s, with detection of 214 nm. Anal. recovery, as tested with three lots of CN sorbent, ranged 47-95% for the 10 cyclosporines. Between-run coeffs. of

variation are <10% at 200 .mu.g/L (concn. of each compd.) and the std. curves are linear to 1500 .mu.g/L. A study of the sepn. mechanisms are reported.

ST cyclosporine metabolite blood HPLC; liq chromatog cyclosporine metabolite blood

IT Blood analysis

(cyclosporine and metabolites detn. in human, by HPLC)

IT Bile

(cyclosporine metabolites purifn. from human)

IT Chromatography, column and liquid

(high-performance, of cyclosporine and metabolites in human blood)

IT 59865-13-3, Cyclosporine A 59865-13-3D, Cyclosporin A, metabolites

89270-23-5 89270-25-7 89270-26-8 89270-28-0 89270-29-1

100364-58-7 107335-27-3 107335-28-4

RL: ANT (Analyte); ANST (Analytical study)

(detn. of, in human blood by HPLC)

L44 ANSWER 28 OF 29 HCAPLUS COPYRIGHT 2002 ACS

AN 1986:564395 HCAPLUS

DN 105:164395

TI Mass spectrometric analysis of cyclosporine metabolites

AU Hartman, N. R.; Jardine, I.

CS Dep. Pharmacol., Mayo Clin., Rochester, MN, 55905, USA

SO Biomedical & Environmental Mass Spectrometry (1986), 13(7), 361-72

CODEN: BEMSEN; ISSN: 0887-6134

DT Journal

LA English

CC 1-2 (Pharmacology)

AB Sensitive mass spectrometric techniques were developed to det. the structure of metabolites of cyclosporine (CsA) [59865-13-3]. First, the mol. wt. of the metabolite was detd. by using fast atom bombardment mass spectrometry or thermospray liq. chromatog./mass spectrometry. The metabolite is then hydrolyzed to its component amino acids, which were esterified and acylated and identified by gas chromatog./mass spectrometry. To distinguish metab. at the 4 identical N-Me leucines, the metabolite was partially hydrolyzed, the resulting peptides were derivatized to the trimethylsilylpolyamino alcs., and these in turn were analyzed by gas chromatog./mass spectrometry. These procedures were used to det. the structure of metabolites of CsA isolated from rabbit bile. The detn. of the structure of one metabolite carboxylated on the .eta.-carbon of amino acid 1, and of one metabolite hydroxylated on the .eta.-carbon of amino acid 1 and on the .gamma.-carbon of N-Me leucine 9 is presented. These procedures should be generally useful for the structural anal. of microgram amts. of CsA metabolites and analogs.

ST cyclosporine metab bile mass spectrometry; mass spectrometry cyclosporine metabolite

IT Bile

(cyclosporine metab. by)

IT 89270-24-6 89270-26-8 89270-28-0 100364-58-7

RL: BIOL (Biological study)

(as cyclosporine metabolite, structure elucidation by mass spectrometry of)

IT 89270-25-7 104671-68-3 104671-69-4 104671-70-7 104696-98-2

RL: PRP (Properties)

(mass spectra of)

IT 59865-13-3

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(metab. of, by bile, metabolite structure detn. by mass spectrometry after)

L44 ANSWER 29 OF 29 HCAPLUS COPYRIGHT 2002 ACS

AN 1986:81480 HCAPLUS  
DN 104:81480  
TI An acid metabolite of cyclosporine  
AU Hartman, Neil R.; Trimble, Laird A.; Vederas, John C.; Jardine, Ian  
CS Dep. Pharmacol., Mayo Clin., Rochester, NY, 55905, USA  
SO Biochemical and Biophysical Research Communications (1985),  
133(3), 964-71  
CODEN: BBRCA9; ISSN: 0006-291X  
DT Journal  
LA English  
CC 1-2 (Pharmacology)  
AB The primary biliary metabolite of cyclosporine (I) was isolated from  
rabbit and human bile. The material was identified by mass spectrometry  
and by NMR spectrometry as the .alpha.,.beta.-unsatd. carboxylic acid I  
deriv. [100364-58-7] in which the N-Me group of the  
cyclosporine-specific 9 C amino acid is oxidized to an .alpha., .beta.  
unsatd. carboxylic acid functionality. This major cyclosporine metabolite  
is inactive in a phytohemagglutinin-stimulated lymphocyte proliferation  
assay.  
ST cyclosporine metabolite identification spectrometry NMR; bile cyclosporine  
metabolite  
IT Bile  
(cyclosporine metabolite detn. in, of humans and lab. animals, by mass  
spectrometry and NMR)  
IT Immunosuppression  
(cyclosporine metabolite in relation to)  
IT 100364-58-7  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
study, unclassified); BIOL (Biological study)  
(as cyclosporine metabolite, in bile of humans and lab. animals,  
identification and activity of)

=> fil uspatall

FILE 'USPATFULL' ENTERED AT 15:35:10 ON 12 DEC 2002  
CA INDEXING COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 15:35:10 ON 12 DEC 2002  
CA INDEXING COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

=>

=> d bib abs hitrn tot 145

L45 ANSWER 1 OF 3 USPATFULL  
AN 2002:259374 USPATFULL  
TI Cyclosporins for the treatment of respiratory diseases  
IN Or, Yat Sun, Cambridge, MA, UNITED STATES  
Lazarova, Tsvetelina, Brookline, MA, UNITED STATES  
PI US 2002142946 A1 20021003  
AI US 2001-800856 A1 20010305 (9)  
DT Utility  
FS APPLICATION  
LREP SANDHYA L. KALKUNTE, ENANTA PHARMACEUTICALS, INC., 500 ARSENAL STREET,  
WATERTOWN, MA, 02472  
CLMN Number of Claims: 11  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 945  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB The present invention relates to novel semisynthetic cyclosporin analogs  
of Formula (I): ##STR1##

X is absent, --C1-C6 alkyl-, or --C3-C6 cycloalkyl-

Y is selected from the group consisting of:

(i) C(O)--O--R1, where R1 is hydrogen, C1-C6 alkyl, optionally substituted with halogen, heterocyclic, aryl, C1-C6 alkoxy, C1-C6 alkylthio, halogen-substituted C1-C6 alkoxy, or halogen-substituted C1-C6 alkylthio;

(ii) C(O)--S--R1, where R1 is as previously defined;

(iii) C(O)--OCH.sub.2--OC(O)R2, where R2 is C1-C6 alkyl, optionally substituted with halogen, C1-C6 alkoxy; C1-C6 alkylthio, heterocyclic or aryl;

(iv) C(S)--O--R1, where R1 is as previously defined, and

(v) C(S)--S--R1, where R1 is as previously defined;

B is -.alpha.Abu-, -Val-, -Thr- or -Nva-; and

U is -(D)Ala-, -(D)Ser-, --[O--(2-hydroxyethyl)(D)Ser]-, --[O-acyl(D)Ser]- or --[O--(2-acyloxyethyl)(D)Ser]-.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 100364-58-7P 457612-98-5P 457612-99-6P  
 457613-00-2P 457613-01-3P 457613-02-4P  
 457613-03-5P 457613-04-6P 457613-05-7P  
 457613-06-8P 457613-07-9P 457613-08-0P  
 457613-09-1P 457613-10-4P 457613-11-5P  
 (cyclosporins for the treatment of respiratory diseases)  
 IT 122547-85-7P  
 (cyclosporins for the treatment of respiratory diseases)

L45 ANSWER 2 OF 3 USPATFULL

AN 95:58066 USPATFULL

TI Fluorescence polarization assay for cyclosporin A and metabolites and related immunogens and antibodies

IN Wang, Nai-Yi, Mundelein, IL, United States

Wang, Philip P., Libertyville, IL, United States

Morrison, Marjorie A., Grayslake, IL, United States

PA Abbott Laboratories, Abbott Park, IL, United States (U.S. corporation)

PI US 5427960 19950627

AI US 1994-318570 19941005 (8)

RLI Continuation of Ser. No. US 1993-60598, filed on 12 May 1993, now abandoned which is a division of Ser. No. US 1991-776890, filed on 15 Oct 1991, now patented, Pat. No. US 5239057 which is a continuation of Ser. No. US 1989-376244, filed on 6 Jul 1989, now abandoned which is a continuation of Ser. No. US 1987-31494, filed on 27 Mar 1987, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Chan, Christina Y.

CLMN Number of Claims: 3

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 810

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to a fluorescence polarization immunoassay for cyclosporin A and metabolites thereof. The present invention also relates to novel cyclosporin A derivative compounds useful in fluorescence polarization techniques. Included among the novel compounds are cyclosporin A derivatives where the amino acid in the

first position is altered. The cyclosporin A derivatives are useful in forming immunogens for raising antibodies specific to cyclosporin A and metabolites thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 122547-85-7P 122547-86-8P

(prepn. of, in cyclosporin A-aminomethylfluorescein conjugate prepn.)

L45 ANSWER 3 OF 3 USPATFULL

AN 93:69983 USPATFULL

TI Fluorescence polarization assay for cyclosporin a and metabolites and related immunogens and antibodies

IN Wang, Nai-Yi, Mundelein, IL, United States

Wang, Philip P., Libertyville, IL, United States

Morrison, Marjorie A., Grayslake, IL, United States

PA Abbott Laboratories, Abbott Park, IL, United States (U.S. corporation)

PI US 5239057 19930824

AI US 1991-776890 19911015 (7)

RLI Continuation of Ser. No. US 1989-376244, filed on 6 Jul 1989, now abandoned which is a continuation of Ser. No. US 1987-31494, filed on 27 Mar 1987, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Chan, Y. Christina

LREP Steele, Gregory W., Pope, Lawrence S., Breininger, Thomas M.

CLMN Number of Claims: 7

ECL Exemplary Claim: 5

DRWN No Drawings

LN.CNT 771

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to a fluorescence polarization immunoassay for cyclosporin A and metabolites thereof. The present invention also relates to novel cyclosporin A derivative compounds useful in fluorescence polarization techniques. Included among the novel compounds are cyclosporin A derivatives where the amino acid in the first position is altered. The cyclosporin A derivatives are useful in forming immunogens for raising antibodies specific to cyclosporin A and metabolites thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 122547-85-7P 122547-86-8P

(prepn. of, in cyclosporin A-aminomethylfluorescein conjugate prepn.)

=> d his

(FILE 'HCAPLUS' ENTERED AT 14:18:09 ON 12 DEC 2002)

DEL HIS

E OR Y/AU

L1 105 S E4-E8

E LAZAROVA T/AU

L2 30 S E3-E11

E ENANTA/PA,CS

L3 13 S E3-E9

L4 137 S L1-L3

L5 5 S L4 AND ?CYCLOSPOR?

SEL DN AN 1 2

L6 2 S L5 AND E1-E4

SEL RN

FILE 'REGISTRY' ENTERED AT 14:21:00 ON 12 DEC 2002

L7 21 S E5-E25

L8 17 S L7 AND SQL/FA

L9 STR  
L10 32 S L9  
L11 685 S L9 FUL  
SAV L11 LIU800/A  
L12 727 S ['ABU' 'NVA' VT] 'SAR' LVLA[AS] LLV/SQSP  
L13 342 S L11 AND L12  
L14 342 S L13 AND 11/SQL  
L15 STR L9  
L16 11 S L15 CSS SAM SUB=L14  
L17 224 S L15 CSS FUL SUB=L14  
SAV L17 LIU800A/A  
L18 STR L15  
L19 9 S L18 CSS SAM SUB=L17  
L20 166 S L18 CSS FUL SUB=L17  
SAV L20 LIU800B/A  
L21 STR L9  
L22 STR L21  
L23 0 S L22 SAM SUB=L20  
L24 2 S L22 FUL SUB=L20  
L25 STR L22  
L26 126 S L25 FUL SUB=L20  
SAV L26 LIU800C/A  
L27 11 S L26 AND (LAELED OR IDS/CI OR (D OR T)/ELS OR 11C# OR 13C# OR  
L28 115 S L26 NOT L27  
L29 27 S L28 AND NC>=2  
L30 21 S L28 AND NR>=3  
L31 82 S L28 NOT L29,L30  
L32 1 S L31 AND MULTICHAIN/NTE  
L33 81 S L31 NOT L32  
L34 65 S L33 NOT L8  
L35 12 S L34 AND (C64H113N11015 OR C69H114N12017 OR C68H116N12016 OR C  
SEL RN L35 2 5 7-12  
L36 4 S L35 NOT E26-E33  
SEL RN 4  
L37 3 S L36 NOT E34  
L38 20 S L8,L37  
SAV L38 LIU800D/A

FILE 'HCAOLD' ENTERED AT 15:32:02 ON 12 DEC 2002  
L39 0 S L38

FILE 'USPATFULL, USPAT2' ENTERED AT 15:32:05 ON 12 DEC 2002

FILE 'REGISTRY' ENTERED AT 15:32:24 ON 12 DEC 2002  
SEL RN L8 17  
L40 16 S L8 NOT E35

FILE 'HCAPLUS' ENTERED AT 15:32:57 ON 12 DEC 2002.  
L41 29 S L40 OR L37  
L42 1 S L41 AND L4  
L43 28 S L41 AND (PD<=20010305 OR PRD<=20010305 OR AD<=20010305)  
L44 29 S L41-L43

FILE 'USPATFULL, USPAT2' ENTERED AT 15:33:58 ON 12 DEC 2002  
L45 3 S L40 OR L37

FILE 'REGISTRY' ENTERED AT 15:34:17 ON 12 DEC 2002

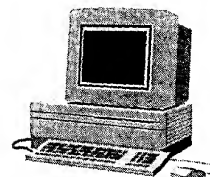
FILE 'HCAPLUS' ENTERED AT 15:34:49 ON 12 DEC 2002

FILE 'USPATFULL, USPAT2' ENTERED AT 15:35:10 ON 12 DEC 2002

# BioTech-Chem Library

## Search Results

### Feedback Form (Optional)



Scientific & Technical Information Center

The search results generated for your recent request are attached. If you have any questions or comments (compliments or complaints) about the scope or the results of the search, please contact *the BioTech-Chem searcher* who conducted the search *or contact*:

**Mary Hale, Supervisor, 308-4258**  
CM-1 Room 1E01

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#### *Voluntary Results Feedback Form*

➤ *I am an examiner in Workgroup:* (Example: 1610)

➤ *Relevant prior art **found**, search results used as follows:*

- ☐ 102 rejection
- ☐ 103 rejection
- ☐ Cited as being of interest.
- ☐ Helped examiner better understand the invention.
- ☐ Helped examiner better understand the state of the art in their technology.

*Types of relevant prior art found:*

- ☐ Foreign Patent(s)
- ☐ Non-Patent Literature  
(journal articles, conference proceedings, new product announcements etc.)

➤ *Relevant prior art **not found**:*

- ☐ Results verified the lack of relevant prior art (helped determine patentability).
- ☐ Search results were not useful in determining patentability or understanding the invention.

**Other Comments:**

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Drop off completed forms at the **Circulation Desk CM-1**, or send to Mary Hale, **CM1-1E01** or e-mail **mary.hale@uspto.gov**.